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4

Use of Biological Markers in Assessing Human Exposure to Airborne Contaminants

INTRODUCTION

As used in this report, biological markers are indicators of changes or events in human biological systems. For example, a metabolite of some exogenous substance found in a person's blood or urine might be considered a marker of the person's exposure to that substance in the environment. If a tissue response to the person's exposure to the substance parallels a disease process, but does not itself constitute a disease process, the tissue response might be considered a marker of effect. The use of biological indicators of exposure to toxic substances is not a new concept—it has been used in occupational health monitoring for many decades. However, as the emphasis on conducting accurate exposure assessments increases, biological markers of exposure will be used more frequently. A dramatic indicator, particularly in occupational epidemiology studies, is death. Less drastic and more manipulable biological measures of health outcome do exist and continue to be developed.

Unfortunately, terminology is confusing, the array of technological subtleties is bewildering, and there is a potential for ethical dilemmas. By virtue of their collaborative and interdisciplinary nature, investigations involving biological markers are highly demanding in terms of personnel, cost, and effort to develop mutual understanding between researchers in different fields. Incorporation of biological markers into exposure assessment engenders new and significant methodological problems in the design of studies that use human subjects and in analysis of data. It also introduces important ethical questions into health effects research, particularly when information on biological markers of uncertain relation to adverse health effects is given to a possibly exposed person. Successful use of biological markers will require an understanding of the fate and effects of a contaminant within a person to permit the

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relation of marker data to the exposure and the establishment of relationships among biological markers of effect and exposure.

This chapter discusses how biological markers might be used as surrogates for or in combination with other measures of exposure, including comments on their limitations.

FROM EXPOSURE TO HEALTH EFFECTS: KINDS OF MARKERS

As defined in Chapter 1, exposure to an airborne contaminant is the product of the concentration of the contaminant and the period during which exposure is at that concentration. "Dose" is defined as the actual amount of a given contaminant that is absorbed or deposited in the body of an exposed organism in a given period (usually with reference to a single medium or route of exposure). "Potential dose" assumes total absorption of a contaminant. The term dose can be subdivided into internal dose and biologically effective dose—both are discussed in this chapter with regard to biological markers. "Effect" is defined as an adverse health outcome or nuisance resulting from exposure. An exposure might or might not lead to a dose, and a dose to a health or nuisance effect. Each of these compartments may also be subdivided into stages representing a progression from exposure to adverse health effect, as shown in Figure 1.2 in Chapter 1. These stages are not discrete. The progression from exposure to effect is a result of the physiological changes that can occur within the organism. The progression can be affected at any point by internal biological factors or by external interventions.

The classes of biological markers are depicted in Figure 4.1, an elaboration of Figure 1.2 in Chapter 1. Biological markers can be used for each stage in the progression and can be used either to determine the exposure to the causative agent or to predict adverse health effects (Committee on Biological Markers of the National Research Council, 1987). Markers can be divided into three broad classes: markers of exposure, markers of health effects, and markers of susceptibility (NRC, 1989). The committee focuses in this chapter on the application of biological markers to assessment of exposure to contaminants rather than their use to predict health effects. However, the use of markers to predict health effects should not be disregarded.

As discussed in Chapter 1, biological markers of exposure integrate all routes of exposure to a particular contaminant. For example, lead concentrations as measured in a human tissue, such as blood, can reflect exposure via any or all of such routes, including inhalation of lead in ambient air, ingestion of vegetables contaminated by deposition of airborne lead and ingestion of

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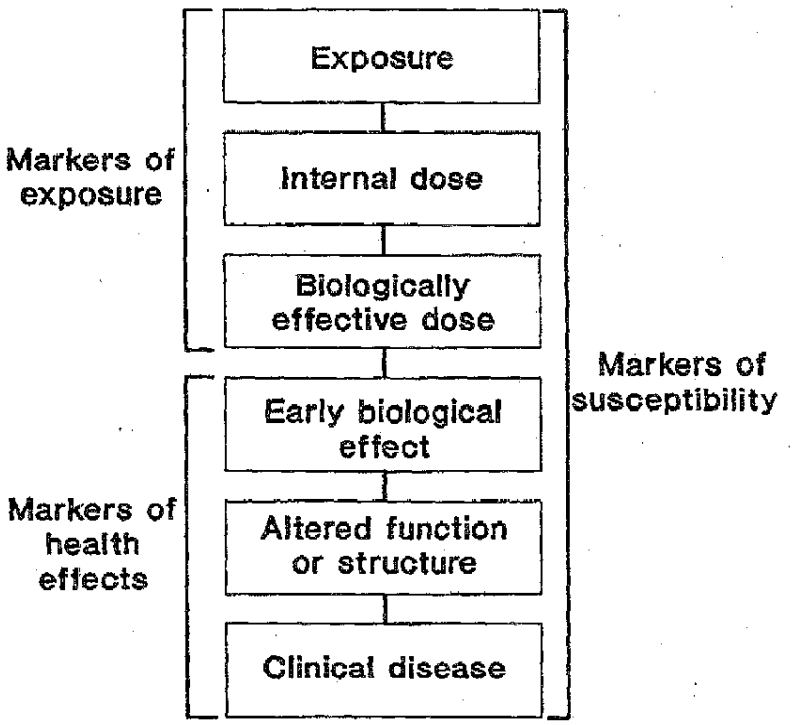

FIGURE 4.1 Kinds of biological markers. Source: Adapted from Committee on Biological Markers, 1987.

lead in drinking water or dust, especially by children with pica. This integrating process of biological markers of exposure can be important for risk assessment and risk management. In the case of lead, for example, the amount inhaled might be assessed with procedures described in Chapter 3. If only a very small portion of the observed dose of lead could be accounted for via inhalation, other exposure routes and sources might then be sought.

Biological markers provide information on dose that can be related to exposure by using pharmacokinetic or pharmacodynamic models (e.g., blood lead or carboxyhemoglobin). Internal dose is the amount of contaminant that is absorbed into the body in a given period. Biological markers of internal

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dose directly measure the exposure substance or its metabolites in cells, tissues, or body fluids. The biologically effective dose is the amount of contaminant or its metabolites that has interacted with a target site over a given period so as to alter a physiological function. Such an interaction can lead to disease or be subjected to repair.

Biological markers of health effects (referred to in this chapter as biological markers of effect) represent a further step away from exposure and a step closer to the clinical manifestation of disease. A marker of early biological effect provides information on an event resulting from a toxic interaction, either at a target or at an analogous site. An early effect is considered an irreversible step in pathogenesis or a qualitative or quantitative correlate of a disease process. Biological markers of effect also include preclinical alterations in organs, tissue structure, or function directly associated with disease. To be useful in disease prevention, these markers of effect should be measurable at preclinical stages.

Biological markers of susceptibility span the entire range of markers shown in Figure 4.1. They indicate an organism's inherent or acquired limitations that affect its response to an exposure to a particular contaminant. These markers can be useful in understanding the relationships that exist between markers of exposure and effect.

Relating a biological marker directly to an exposure becomes more uncertain as one obtains information on the stages within the progression shown in Figure 4.1. Accordingly, the Committee on Biological Markers of the National Research Council (1987) has stated that "markers of health effects are often less readily related to environmental exposures than are the markers of exposure." Therefore, greater emphasis is given to markers of exposure. Biological markers of effect can be used for exposure analysis if and only if information concerning contaminant identity and route of exposure is incorporated into the exposure assessment.

An attempt to use biological markers as surrogates for measurements of exposure might raise ethical questions. When humans are directly involved in biological-marker studies, caution must be exercised in reporting results to study subjects, to avoid undue psychological stress when the significance of the marker for future adverse health effects is uncertain (Ashby, 1988).

Pharmacokinetics is the quantitative description of the rates of absorption, distribution, metabolism, and elimination of a contaminant taken into a biological system (Leung and Pastenbach, 1988). Pharmacodynamics is the description of the processes that relate biologically effective dose to health effects. Pharmacokinetic modeling techniques are used to aid in the extrapolation of test results from animals to humans; pharmacodynamic models are just being developed (Menzel, 1987). The pharmacokinetic models attempt to

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compensate in part for the physiological and biochemical differences between humans and test animals, which can cause markedly different responses to the same substance. The models use mechanistic, biochemical, and physiological information to describe the disposition of a contaminant once taken in. Mechanistic studies provide information on the target tissues, metabolic pathways, and nature of a contaminant's chemically stable metabolites or reactive intermediates. Pertinent biochemical data include partition coefficients and permeation coefficients. Pertinent physiological factors include tissue volumes, blood flow rates, and ventilation rates. Much of this information can be obtained from published sources or through the use of in vitro techniques.

A physiologically based pharmacokinetic model is constructed as a set of biologically defined compartments—tissues and target organs are grouped into well-perfused, moderately perfused, or poorly perfused compartments for describing the process of metabolic transformation in the lungs, kidneys, or liver. Each compartment has a defined volume, blood flow, partition coefficient, and metabolic constants (Travis et al., 1990). The growing availability of sophisticated simulation packages that can solve large numbers of mass-balance differential equations makes the construction and testing of models increasingly easier.

An example of use of pharmacokinetic techniques to relate various biological markers to each other and to an exposure is the study of halothane concentrations in the breathing zone and blood of operating-room personnel (Fiserova-Bergerova, 1987). Anesthesiologists had the highest breathing-zone concentrations but lower blood concentrations than nurses, who had substantially lower breathing-zone concentrations. Pharmacokinetics accounted for the difference: the anesthesiologists had a primarily sedentary job, whereas the nurses were actively moving about the room and therefore had higher ventilation rates and cardiac output.

Pharmacokinetics and pharmacodynamics can also be used to indicate which tissues are to be sampled and when samples should be taken, as discussed in Chapter 2. For example, the pharmacokinetics of cadmium indicate that, if one is interested in recent cadmium exposure, one should analyze blood; if accumulation is of interest, one should analyze urine (ACGIH, 1986). Another study involved the effect of ethylene glycol ethers on sperm count. Pharmacodynamic studies did not show a relationship between sperm count and methoxyacetic acid, the primary metabolite of ethylene glycol ethers (Smith, 1988). However, because the sperm production cycle takes 80 days, there is a lag of approximately 80 days between toxic exposure and reduced sperm count. Therefore, exposure and effect measurements had to be offset by approximately 80 days.

An understanding of the pharmacokinetics of a contaminant is important

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in relating biological markers to the original exposure. As pharmacodynamic modeling advances, relationships will then be established between biological markers of exposure and biological markers of effect (Menzel, 1987).

APPLICATIONS OF HUMAN BIOLOGICAL MARKERS

Markers of Exposure

Sensitive physicochemical methods can detect and measure very low concentrations of xenobiotic substances in the body (Sheldon et al., 1986). They are being used in industrial hygiene with biologic exposure indexes as reference values for workplace exposure monitoring (ACGIH, 1986, 1988b; Fiserova-Bergerova, 1987). Concentrations of a contaminant are usually measured in exhaled air, blood, or urine, but breast milk and semen have also been used. Each biological medium has a unique relevance to exposure and health outcome, and interpretation of the resulting data requires an understanding of the pharmacokinetics of the substance in question. For example, concentrations in exhaled air generally reflect only inhalation, whereas concentrations in blood, other tissues, and other fluids might reflect recent exposures from several sources and stored body burdens.

Measures of internal dose can be characterized according to chemical specificity and selectivity. Highly selective markers of exposure typically represent measures of unchanged contaminants in biological media and thus provide the most clear-cut evidence of a specific environmental exposure. Studies of volatile airborne contaminants usually involve the measurement of a specific substance in exhaled air. The unchanged compound or its metabolite in urine may also be analyzed where variations in urinary volume can be accounted for by normalizing the concentration of the analyte to the creatinine levels. If it is necessary to analyze for a metabolite, rather than its parent substance, a procedure can lose some specificity in relating the biological marker to exposure. For example, exposure to styrene and exposure to ethyl benzene each give rise to mandelic acid in urine, so a finding of mandelic acid in urine would have to be supplemented with another assay (e.g., of breath) to determine which compound the subject was exposed to.

Measures of biologically effective dose include DNA and hemoglobin adducts in peripheral blood and other cells and tissues—e.g., lung macrophages, sputum, bronchial washes or bronchoalveolar lavage fluid, buccal mucosa, bone marrow, placental tissue, and lung tissue. Such measures can be used as markers of exposure only when the analyzed cells or tissues are the target of the exposure contaminant or its metabolites. Many carcinogens and repro-

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ductive toxicants are metabolically activated to electrophilic metabolites that covalently bind to DNA. Adducts on DNA, if they occur at critical sites and are not repaired, can cause gene mutation, which has been shown to be an initiating step in the multistage carcinogenic process. Several methods to detect DNA-chemical adducts in lymphocytes and target tissues are available, including radio- or enzyme-linked immunoassays that use polyclonal or monoclonal antibodies, ^{32}P-postlabeling, and synchronous fluorescence spectrophotometry (Watson, 1987; Santella, 1988).

The first use of antibodies to detect polycyclic aromatic hydrocarbon (PAH)-DNA adducts involved lung tissue and peripheral white blood cells from lung-cancer patients and controls (Perera et al., 1982). They have since been used to analyze white blood cells and other tissues from persons exposed to PAHs in cigarette smoke and in occupational settings (e.g., foundries and coke ovens) (Harris et al., 1985; Shamsuddin et al., 1985; Haugen et al., 1986; Perera et al., 1988). Antibodies are available to assess formation of DNA adducts in humans with several carcinogenic substances: aflatoxin B_1, benzo*a*pyrene (BaP) and other PAHs, cisplatinum, and methoxypsoralen. Immunoassays can detect frequencies as low as one adduct per 10^8 nucleotides. Assays that use monoclonal antibodies are highly specific for a given substance, but those with polyclonal antibodies, such as PAH-DNA antibodies, can react with multiple structurally related compounds and thus lose specificity. The value of immunoassays depends on the development of appropriate antibodies, and the highly specific monoclonal assays can be time-consuming and technically difficult.

In contrast with the monoclonal assays, ^{32}P-postlabeling can be used to recognize various adducts without characterizing their chemical compositions. It can be more sensitive than monoclonal assays; it can detect one adduct per 10^{10} nucleotides. The method produces an image that constitutes an idiosyncratic "fingerprint" of the exposure. However, researchers developing this assay have faced difficulties in identifying the adducts formed. If the adducts can be isolated and identified, further analyses can be carried out with immunoassay techniques, once the appropriate antibody has been developed. The postlabeling method generally is limited to the measurement of bulky adducts that might limit the usefulness of the technique to smaller airborne contaminants, and the results of the method are only semiquantifiable. Effective use of the postlabeling method requires the synthesis of an internal standard since the efficiency of labeling can vary according to the substance.

The technique of ^{32}P-postlabeling has been applied to the identification of various alkylating and methylating agents (Reddy and Randerath, 1987). It is possible to characterize methylating agents using HPLC (high performance liquid chromatography); however, this is not a routine technique. Application

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to populations exposed to airborne pollutants has been limited to assessment of BaP and other PAH exposure of foundry workers and roofers (Hemminki et al., 1988; Phillips et al., 1988). Some investigators have related placenta and lung adduct measurements to cigarette smoking with postlabeling techniques (Everson et al., 1986); others have not seen smoker-nonsmoker differences in bone marrow, white blood cells, or buccal mucosa (Dunn and Stich, 1986; Phillips et al., 1986; Jahnke et al., 1990).

A third approach uses synchronous fluorescence spectrophotometry, which has recently been applied to coke-oven workers with a reported sensitivity of one BaP adduct per 10^7 nucleotides (Vahakangas et al., 1985). The method has been used to confirm the presence of BaP-DNA adducts in placental tissue from smokers (Weston et al., 1988). HPLC and fluorescence spectroscopy have been used to detect excised carcinogen-DNA adducts in urine (Autrup et al., 1983). The technique is limited in that it is useful only for detecting compounds that fluoresce, such as PAHs.

Assays that measure protein adducts, including adducts of direct binding agents and metabolites with hemoglobin, can in some cases be a good surrogate for DNA-adduct measurements. That use is supported by correlations in animal studies between protein and DNA binding by BaP, vinyl chloride, ethylene oxide, methyl methanesulfonate, and *trans*-4- dimethylaminostilbene (IARC, 1984; Neumann, 1984; Bartsch, 1988). Methods available for measuring those adducts include immunoassays, amino acid analysis by ion-exchange LC, and the combination of gas chromatography and mass spectrometry (GC-MS) with both conventional ionization and negative chemical ionization techniques. GC-MS has been successfully applied to the quantitation of 4-aminobiphenyl (4-ABP) hemoglobin adducts in smokers (Bryant et al., 1987; Perera et al., 1987). Sensitive GC-MS methods can measure protein adducts in persons exposed to ethylene oxide from cigarette smoke and workplace sources (Osterman-Golkar et al., 1984; Farmer et al., 1986; Törnqvist et al., 1986). Because of the 3-month life span of hemoglobin, those assays reflect relatively recent exposures; DNA adducts in lymphocyte subpopulations reflect exposure integrated over a longer period. Protein adducts are more abundant than their DNA counterparts and therefore provide a more sensitive measure of exposure.

Markers of Effect

Markers of biological effect can be useful for exposure assessment, provided that they can be related to the exposure responsible for an effect. A number of markers might signal a preclinical or presymptomatic stage in disease

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development, some of which are specific to a chemical; others might signal adaptive changes that are not themselves pathological. For example, the presence of carboxyhemoglobin in the blood signals that damage related to carbon monoxide exposure is occurring, but the source could be the inhalation of carbon monoxide or the metabolism of methylene chloride. Red blood cell delta-aminolevulinic acid dehydratase (delta-ALAD) has been used as an indicator of early toxic effects of lead exposure (Friberg, 1985), but the American Conference of Governmental Industrial Hygienists (ACGIH) has not recommended its use as a biological exposure index, because of "interpretative difficulties" (ACGIH, 1986). Reduction in plasma acetylcholinesterase activity has been specifically linked to organophosphate insecticides, but thiocarbamates can induce the same effect (Fiserova-Bergerova, 1987). Nonspecific markers of reproductive impairment include plasma ollicle-stimulating hormone, plasma luteinizing hormone, salivary progesterone, and urinary hydroxyproline or hydroxylysine (which could reflect tissue remodeling (collagen turnover) after inhalation exposure to environmental pollutants) (NRC, 1988).

Cytogenetic techniques provide another direct, although nonspecific, method of identifying changes that occur on the chromosomal level after exposure to environmental contaminants. Cytogenetic changes include alterations in chromosome number, such structural chromosomal changes as breakage and rearrangement, and exchanges between reciprocal portions of a single chromosome referred to as sister-chromatid exchanges (SCE). The mechanism responsible for inducing SCEs is not well understood. Many classes of carcinogens and mutagens are known to increase SCE frequency, and that could limit the usefulness of SCE frequency for exposure assessment. For example, increased SCE frequency has been found in workers exposed to ethylene oxide, styrene, benzene, arsenic, chloromethyl ether, chloroprene, organophosphates, or ionizing radiation (Evans, 1982).

Chromosomal aberrations have been used successfully as a biological dosimeter to measure absorbed radiation in humans (IAEA, 1986); however, ionizing radiation acts through mechanisms that are different from those of most other atmospheric contaminants. Micronuclei, fragments of nuclear material left in the cytoplasm after replication, are considered an indication of the prior existence of chromosomal aberrations. Cytogenetic markers can be identified in lymphocytes and sometimes in other tissue with stimulated cell culture and staining techniques in conjunction with light microscopy (Livingston et al., 1983; Carrano and Natarajan, 1988). Many types of human cancers are associated with specific alterations (e.g., adult leukemia) or nonspecific aberrations, and there is increasing evidence that chromosomal aberrations might be linked to the carcinogenic process related to exposure to some chemicals (Yunis, 1983).

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New techniques have been based on the fact that a specific mutagen (such as a chemical agent) induces a specific pattern of gene mutation (Benzer and Freese, 1958). Techniques have been developed to screen for patterns in genes from human peripheral blood lymphocytes that contain mutations in the non-essential enzyme hypoxanthine guanine phosphoribosyl transferase (HGPRT) (Cariello and Thilly, 1986). One technique involves the use of denaturing gradient gel electrophoresis, which can separate short DNA molecules according to their melting (uncoiling) properties. The melting behavior of the DNA fragments is extremely sequence-dependent; a single base-pair substitution can change migration on the gel. That type of tool provides a convenient means of examining HGPRT for genetic alterations (according to the generation of mutation-related spectra on the gel) and then relating the alterations to specific causative agents (Cariello et al., 1988). The technique depends on the use of a high-fidelity polymerase chain reaction to provide in vitro amplification of a given region of the genome and thus improve sensitivity and provide enough material for sequencing. The application of the technique to exposure assessment holds the potential for being specific for a substance causing mutation and so would be useful in epidemiological studies, risk assessment, and risk management. In addition, it leads to a measure of a biological effect and thus could be more directly related to potential adverse health outcomes than biological markers of exposure. Extensive validation of the technique is necessary.

Another new approach to assessing genetic effects involves measurement of single-strand breaks in lymphocyte DNA. A linear dose-response relationship was found in mice exposed to styrene (Walles and Orsen, 1983), and increased frequencies of breaks were found in workers exposed to styrene (Walles et al., 1988). The assay was also used to demonstrate differential styrene metabolism and clearance by various organ systems (Walles and Orsen, 1983). Alkylating agents, such as *N*-nitroso-*N*-methylnitroguanidine and ethyl methylsulfonate, which are negative in standard cell transformation assays, have also been shown to be strong inducers of single-strand breaks (Lubet et al., 1983).

DNA hyperploidy measured in exfoliated bladder and lung cells has been shown to be a biological marker of response to exposure to carcinogens. It has been detected with flow cytometry of stained cells (Melamed et al., 1977), but this approach requires large samples and cannot be used to evaluate individual cells. The more recently developed technique of quantitative fluorescence image analysis involves the scanning of the fluorescence of individual stained cells in a microscopic field (Hemstreet et al., 1986). This technique has shown DNA hyperploidy to be highly correlated with magnitude of exposure in workers exposed to aromatic amines (Hemstreet et al., 1988). Further

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validation is needed to determine the specificity of DNA hyperploidy markers for causative agents and for actual magnitudes of exposure in the environment.

Activated oncogenes and their protein products can be used as markers of effect. During oncogenesis, a normal segment of DNA (a proto-oncogene) is activated to a form that causes cells to become malignant. Activation can occur through several mechanisms, including gene mutation and chromosomal breaks and rearrangements. Of particular interest in assessment of ambient environmental exposures is the *ras* oncogene, first identified in rat sarcoma, later in human bladder, colon, and lung cancers (Slamon et al., 1984; Spandidos and Kerr, 1984). Activated *ras* oncogenes containing a point mutation have been produced in vitro by a number of ambient pollutants, including BaP, dimethylbenzanthracene, and *N*-nitroso compounds (Sukumar et al., 1984). Activation of the *ras* oncogene can be measured with complex immunoblotting techniques. A more convenient and relatively simple method involves measurement of the gene's abnormal protein product, designated P21. P21 can be measured in tissue or sputum with monoclonal antibodies, as well as in blood and urine with immunoprecipitation techniques. The assay is still in the early validation stage (Brandt-Rauf, 1988). It is likely that more than one oncogene needs to be activated to convert a normal cell to a cancerous one (Stowers et al., 1987). More studies will be needed to reveal the sequential requirements for oncogene activation.

Assays that detect changes in the function of target or analogous tissue, such as decreased sperm counts after dibromochloropropane exposure, provide markers that are closely linked to disease end points. An increased concentration of erythrocyte zinc protoporphyrin (EPP) indicates a later stage in lead toxicity than does delta-ALAD deficiency (Friberg, 1985) and is a better indicator of past chronic exposure to lead then is blood lead concentration (Blumberg et al., 1977; Franco et al., 1984). ACGIH recommends the use of EPP as a measure of lead exposure (ACGIH, 1986), although it points out that iron deficiency can also increase EPP (Lamola and Yamane, 1974).

Some markers can indicate the presence of disease at preclinical or early clinical stages. For example, serum alpha-fetoprotein, although not specific to liver cancer, has been successfully used in China to indicate preneoplasia of the liver (Committee on Biological Markers of the National Research Council, 1987). However, the lack of specificity of tumor markers (such as alpha-fetoprotein) severely restricts their usefulness (Hulka and Wilcosky, 1988).

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UTILITY OF BIOLOGICAL MARKERS

Advantages

Improved Exposure Assessments

Central to establishing the relationship between exposure to a contaminant and the presence of biological markers is the characterization of exposure-dose-effect relationships. Dose used to be determined on the basis of exposure, and the principal limiting factors were the quality and quantity of exposure data for a particular contaminant from all possible sources. Exposure data were obtained primarily from historical records of ambient or workplace monitoring, mathematical modeling, and questionnaires, and not from measurements. The underlying assumption that all persons with comparable exposure receive a similar internal or biologically effective dose is incorrect, as has been shown, for example, in studies of halothane uptake by operating-room personnel. Uptake, absorption, and distribution of a substance can vary with sex, age, health status, diet, hormonal status, and presence of other environmental exposures (Committee on Biological Markers of the National Research Council, 1987). Biological markers help to compensate for many of those variables by integrating all routes of exposure and not only permit individual exposure assessments, but also support estimation of individual biologically effective doses. Thus, when combined with inhalation exposure assessments, biological markers can be used to indicate whether, for instance, inhalation is a major or minor source of a contaminant.

Properly measured, biological markers can reduce misclassification error as to degree of exposure and can increase the power of epidemiological studies to identify associations between exposure and disease. Persons who are highly susceptible to effects from exposure contaminants could be identified in terms of biologically effective dose or early biological effect.

Biological markers also have the potential to differentiate the effects of varied exposure patterns. For example, experimental studies have suggested that induction of heritable mutations by ethylene oxide exposure can vary with dose rate (Generoso et al., 1986).

Validation of Pharmacokinetic Models

Biological markers can, in theory, be useful in developing and validating pharmacokinetic models aimed at relating external exposure to dose (NRC, 1989). As discussed previously in this chapter, pharmacokinetic models have

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been developed in experimental animals and then adjusted for physiological characteristics of humans to permit extrapolation across species and from different doses to dose in humans. They are often based on limited experimental data for which parallel information in humans is lacking. Therefore, direct measurements of dose in experimental animals and humans would allow more valid comparisons between animal models and humans for purposes of risk assessment. For example, the combination of measurement of alveolar styrene, personal workplace monitoring data, blood styrene content, and urinary mandelic acid content can provide an accurate description of styrene uptake, metabolism, and elimination under different conditions of exertion (Droz and Guillemin, 1983).

Detailed modeling approaches are now being used to determine biologically effective dose. Young and Kadlubar (1987) used a three-compartment model to predict the release of the N-OH arylamines in the bladder lumen and the formation of arylamine-DNA adducts in blood as markers of biologically effective dose. This model is being validated in dogs given radiolabeled amino biphenyl.

The ability of doses in surrogate tissues to model the dose received by a target tissue has been assessed in studies involving ethylene oxide. At issue was whether adducts of hemoglobin reflected the dose to DNA in the target cell. Comparison of the alkylation of *N*-(2-hydroxyethyl) histidine in hemoglobin with the alkylation of guanine at the N7 position in DNA from rat livers and testes showed that hemoglobin alkylation gives a reasonable approximation of DNA dose (Osterman-Golkar et al., 1984). Given the degree of alkylation of hemoglobin, it was possible to estimate ethylene oxide exposure during the preceding few months (Calleman, 1984).

Improvement of Risk Extrapolation

Biological markers have the potential to improve risk extrapolation between species and between populations, and to allow better predictions of human risk. Parallel studies of markers, such as biologically effective dose or early response, in experimental animals and human populations can be used to evaluate whether mechanisms or modes of action are similar across species. Given the same substance, the studies can allow calibration of measurements (e.g., chromosomal effects, DNA adducts, or somatic cell mutations) in human populations whose relative risks of cancer are unknown with measurements in experimental animals for which tumor incidences are established.

Comparative monitoring data on several human populations could allow extrapolation from a population whose relative risks of cancer are established

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historically (e.g., cigarette smokers and coke-oven workers) to a population facing similar exposure whose relative risks are unknown.

Finally, validation of molecular markers through parallel in vivo animal and human studies might ultimately provide support for applying marker methods to human cells in culture as a substitute for long-term bioassays as a basis for risk assessment (Perera et al., 1987).

Timely Identification of Persons or Groups at Increased Risk of Disease

Biological markers of exposure and effect can provide an early warning of hazard or potential risk of disease. In general, they can signal the need for greater surveillance or even action to reduce exposure. However, before such action can be taken, a marker must give some indication as to causative agent. For example, if increased blood EPP (indicative of chronic exposure to lead) is observed, greater surveillance could include blood lead measurements to discern recent exposure and to ensure that the EPP concentration is not due to an artifact. Environmental concentrations would also be necessary for assessing whether the exposure route was inhalation, skin absorption, or ingestion, so that appropriate corrective action could be taken.

Biological markers can aid in distinguishing exposure groups and be used to identify eligible participants in "exposure registries," which can be used to assess potential exposures to hazardous substances, e.g., around a toxic-waste dump, explosion, or other untoward event (Schulte and Kaye, 1988). Biological markers of effect indicating altered structure and function should trigger immediate remedial or preventive action, provided that the causative agent and routes can be determined. By providing this information in a timely fashion, in some cases decades before clinical disease would appear, biological markers can be valuable in disease prevention.

Improved Epidemiological Study Design and Inference

Accurate exposure assessments can reduce misclassification error and enhance the power of an epidemiological study. Early biological events are generally more common than disease end points, so markers of effect also expand a study's statistical power (Gann et al., 1985).

Markers permit more cost-effective studies. Appropriately processed tissue samples can be stored in specimen banks, sometimes for long periods, and retrieved for assay when needed later. Specimen banks could be used to

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determine retrospectively whether a particular contaminant was elevated in the general population at an earlier time. This is especially relevant when new analytical techniques are developed with vastly improved sensitivity or specificity.

Other advantages include reduction in time needed for follow up, better characterization of confounders and cofactors, and improved evidence of causal associations.

Disadvantages and Limitations

Lack of Validation

A major limitation of using biological markers for exposure assessments stems from the fact that most are in a developmental stage and not fully validated or field-tested. Methodological problems are similar to those faced in the development of any new technology and include limited availability of standardized protocols and reporting criteria; interlaboratory differences, including variability in quantitation methods and in sensitivity; and the costliness and labor intensiveness of most procedures.

Markers have not yet been developed to study many important environmental exposure-response relationships. For example, nearly all existing markers for carcinogens reflect interaction with somatic genetic material and provide information about the initiation or progression stages in the carcinogenic process. Markers relevant to later events important in the promotion and progression of carcinogenesis are not yet available for human studies.

Ambiguity of Many Markers

A key question regarding biological markers of exposure is, "Given a measured amount of a marker in a specific tissue, what compounds and exposures could have produced the marker?" If multiple compounds can result in the same marker, additional studies might be necessary to reduce the ambiguity. For example, if urinary phenol is indicative of benzene exposure, one must be concerned with other possible sources of phenol in the body that can be related to the use of phenol-containing disinfectants or medications (Fishbeck et al., 1975) or eating meat. Therefore, some other measure of benzene, such as that in end-exhaled air, might be warranted to confirm the exposure. However, on the basis of pharmacokinetics, urinary phenol indicates past exposure, and end-exhaled air only the most recent exposure. The reverse

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situation can also result in ambiguity. If one is using urinary phenol as a specific measure of phenol exposure (in this case, the unchanged analyte, phenol, is the same compound as metabolized benzene), it would require some type of monitoring for benzene (possibly in end-exhaled air) to eliminate that as a possible source of the urinary phenol.

In other instances, multiple compounds might produce the same metabolite, and that could hinder the proper interpretation of the biological marker. Examples of compounds sharing metabolites are styrene and ethyl benzene yielding mandelic acid and tetrachloroethylene and 1,1,1-trichloroethane yielding trichloroacetic acid. If those metabolites where found in urine, additional tests, such as breath measurements, would have to be made to try to determine which compound was involved in the exposure.

Variability of Markers

The goal in assessment of exposure to airborne contaminants is to relate concentration models to exposure models and then to dose models. It is important to know whether similar exposures—i.e., similar products of concentration (c) and time (t)—will result in similar occurrences of biological effect. Yager (1987) exposed rabbits to ethylene oxide at 200 ppm for 6 hr/day, 5 days/week or at 1,500 ppm twice a day for 15 minutes until all groups reached at a specific concentration-time interval (ct) of 7.8×10^4 ppm-hr. If there were a similar relationship between exposure and biological response, various markers would occur with the same frequency, despite the difference in exposure rate. The study showed similar frequencies of *N*-3-(2-hydroxyethyl)histidine in hemoglobin and of sister chromatid exchanges and thus demonstrated Haber's rule of equitoxicity (Haber, 1924): if $c_1t_1 = c_2t_2$, two exposures will produce the same response. The study also showed that the finding is not universal for all biological responses; analysis of rabbit bone marrow smears after a ct of 4.8×10^4 ppm-hr showed mild but consistent degenerative and focal necrotic changes in the group exposed at 1,500 ppm, but not in the other group. Generoso et al. (1986) observed a dose-rate effect for dominant lethal mutations in mice after ethylene oxide exposure. Yager (1987) considers that contradictory findings should be expected, in that they reflect differences in target tissue related to proliferative state, repair capacity, and the likelihood that different genotoxic end points reflect different kinds of damage. The results illustrate the need to evaluate a marker in an appropriate experimental setting before use in the field and to clarify the different effects that occur at different dose rates.

Biological markers can present problems in establishing quantitative rela-

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tionships between exposure and response at low exposures. Examples come from recent research on carcinogen-DNA and carcinogen-protein adducts. Extensive data on DNA, RNA, and protein binding in experimental systems indicate that these macromolecular effects at the lowest administered doses generally follow first-order kinetics; i.e., the degree of initial binding in target organs in vivo is usually directly proportional to presented dose. In some cases, that relationship also holds at very low doses similar to doses that might be encountered by humans as a result of environmental contamination (Neumann, 1984; Wogan and Gorelick, 1985).

Human data on adducts, however, do not demonstrate a proportional relationship between exposure and adduct frequency (response). For example, frequencies of 4-aminobiphenyl (4-ABP) hemoglobin adducts were significantly higher in smokers than in nonsmokers, but there was no significant correlation with amount smoked (Bryant et al., 1987; Perera et al., 1987). That is undoubtedly because of the wide interindividual variation in response to xenobiotic exposure, including nutritional factors (some people ingest anticarcinogens) (Wattenberg, 1983). Variability might also be due to the inability to determine individual exposures precisely when one is dealing with chronic, low, and variable exposures to single or multiple media. However, for ethylene oxide and propylene oxide—unlike PAH and 4-ABP, which must be metabolically activated and for which greater interindividual variability would be anticipated—the frequency of carcinogen-hemoglobin adducts in humans is expected to be reasonably proportional to the estimated dose received. That was indeed the case in the initial study of ethylene oxide-hemoglobin adducts (Calleman et al., 1978), but a later study did not show a correlation between exposure and hemoglobin-adduct frequency (van Sittert et al., 1985), possibly because airborne concentrations of ethylene oxide were very low (less than 0.05 ppm), as would be very likely in a nonoccupational exposure. For workers exposed to propylene oxide, good agreement was seen between the degree of hemoglobin alkylation and estimated propylene oxide exposure (Osterman-Golkar et al., 1984).

Better defined exposure-response relationships were shown by the significant correlation between PAH-DNA adducts measured by immunoassay in peripheral white blood cells from Finnish foundry workers and their occupational exposure to PAH (Perera et al., 1988). Workers were classified as having high (more than 0.2 $\mu g/m^3$), medium (0.05-0.2 $\mu g/m^3$), or low (less than 0.05 $\mu g/m^3$) exposure to BaP (as an indicator PAH). The mean adduct concentrations (in femtomoles of adduct per microgram of DNA) were 1.5 (high-exposure group), 0.62 (medium), 0.24 (low), and 0.066 (controls—unexposed, healthy workers seen at same clinic). These results were corroborated with the postlabeling method carried out on white-cell DNA

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from the same worker population (Hemminki et al., 1988; Phillips et al., 1988). However, despite the correlation between DNA adducts and exposure at the group level, there was significant variation among individuals within the exposed groups. Adducts measured with immunoassay ranged from nondetectable to 2.8 fmol/μg. On the basis of the work of Lioy et al. (1988), it is possible that workers were receiving exposures by other routes, mainly food.

Harris et al. (1985) did not find BaP-DNA adducts in 10 of 41 coke-oven workers evaluated. They suggested that that was probably due to variation in exposure, in individual metabolic balance between activation and deactivation, and in DNA repair capacity. Because DNA repair is both inducible and saturable, differences related to dose are likely (Swenberg et al., 1987; Danheiser et al., 1989).

The manner and timing of sample collection can produce ambiguous or meaningless results. For example, in a study to determine exposure to environmental tobacco smoke with nicotine or its metabolites as markers, different results were obtained when different sampling protocols were used. Physiological pharmacokinetic modeling has demonstrated that the single-time point sampling protocol is of little use, unless a marker has a long half-life, which is rare for most exposures (Schwartz and Balter, 1988). Therefore, a good understanding of the pharmacokinetics is essential for proper timing of sample collection.

Difficulty of Establishing Links Between Exposure and Markers of Effect

Biological markers of effect are usually not exposure-specific. For example, pathophysiological changes, such as alterations in sperm structure or function and hormonal changes indicative of early reproductive disease, are not specific to chemicals and routes of entry. The same is true of most markers of preclinical and clinical immunological, cardiovascular, neurological, and renal dysfunction (EPA, 1988a). With respect to tumorigenesis, most preclinical effect markers—such as fetal proteins, oncogene protein products, structural changes in oncogenes, and chromosomal deletions—do not reveal the identity of the environmental exposure responsible. Increased specificity can be achieved if future studies, such as those suggested by Cariello and Thilly (1986), show that mutagens are specific with regard to the kind and position of mutation, and this specificity can be considered as a chemical fingerprint left on the DNA. The fingerprint would be a powerful tool in establishing the cause-effect relationship. However, Sukumar et al. (1984) observed the same

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ras oncogene is activated in neoplastic cells derived from exposure to several different chemicals, so this lesion cannot act as a fingerprint.

The search for effect markers for pulmonary toxicants is also frustrated by the lack of specificity of pulmonary responses to etiologic agents (NRC, 1988). Those responses include altered breathing patterns and airway constriction, cell injury leading to inflammation, persistent alteration of lung structure (e.g., fibrosis, chronic obstructive pulmonary disease, and granulomatous disease), and neoplasia.

There is a need for research to identify biochemical correlates of structural changes, as well as to distinguish effects caused by a chemical from effects that are responses to cell injury (Smith et al., 1986). It is therefore desirable to incorporate chemical-specific markers of exposure and early biological effect into a study design to complement the nonspecific biological markers. As discussed later, however, relating even a chemical-specific marker to a defined exposure period is not clear-cut.

Confounding Influences on Biological Markers

Biological markers of exposure reflect diverse behavioral, biological, and methodological processes. Hence, they can be more subject to confounding influences than are measurements of ambient airborne contaminants. Droz (1985) evaluated effects of confounding factors on dose with simulation models. He identified six confounding factors that could influence the dose of organic solvents: intraday and interday fluctuation of exposure, repetition of exposure, physical workload, body build, and metabolism. The factors were applied to four solvents (benzene, styrene, methyl chloroform, and tetrachloroethylene) that differ in blood solubility and metabolism. Droz suggested that such models provide a means for assessing the role of confounding factors in internal dose.

Complexity and Resource Intensiveness

By virtue of their collaborative and interdisciplinary nature, biological marker investigations are highly demanding in terms of personnel, cost, and effort to develop understanding among researchers in different fields. Most also require clinical interaction with subjects. Incorporation of biological markers engenders new and important methodological problems in study design and in analysis of data (Schulte, 1987, 1989). It also introduces important ethical questions into health-effects research, particularly if information

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is given to a person concerning a biological marker of effect when the relationship to an adverse health effect is unclear.

Use of Exposure Markers in Conjunction with Traditional Measures

The most effective method of characterizing exposure is to combine methods for assessing ambient exposure with various biological markers (Friberg, 1985). Used together, they enhance the precision and accuracy of exposure information, as exemplified in a study of hospital sterilizer operators occupationally exposed to ethylene oxide (Yager et al., 1983). Ambient and breathing-zone ethylene oxide concentrations were measured, as well as SCEs. Workers were classified into two groups according to estimates of amounts potentially absorbed: low, a mean of 13 mg of ethylene oxide over 6 months; and high, a mean of 500 mg over 6 months. A nonexposed control group was also evaluated. The high-exposure group had a mean of 10.7 SCEs/cell, which was significantly different ($p = 0.002$) from both that in the low-exposure group (7.8 SCEs/cell) and that in the control group (7.6 SCEs/cell). Without the use of ambient measurements to distinguish the two exposure groups, the difference in mean SCE frequency between exposed and control groups would have been only marginally significant ($p < 0.05$).

CRITERIA GOVERNING THE VALIDATION AND USE OF BIOLOGICAL MARKERS

Biological markers can be used to identify discrete components in the exposure-health-effects relationship (Figure 4.1). For a given exposure and disease, it is possible to identify most of the components of the relationship. Whether the relationship is linear or follows some other form, such as a branched network, is uncertain, but the linear concept of a relationship should suffice for research planning. Use of this model, however, should not obscure the need for efforts to explore the relationship between markers that might be represented by more accurate, nonlinear models (see Schulte, 1989, for review).

The current use of biological markers for exposure assessment is not without its pitfalls, and in some cases it cannot occur without adjustments and a stipulation of an independent determination of confounding variables. For example, there will be requirements to account for exposure to background concentrations of contaminants from the same and other media and to adjust

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for seasonal or regional variation in some markers. These adjustments notwithstanding, the conventional techniques for assessing exposure-disease associations, screening for exposure of individuals in populations and handling multiple variables can be practiced for any two components in the relationship (e.g., exposure and internal dose). The major assumption that permits this approach is the causal or positive association between components of the relationship. For investigations involving markers of components from the central regions of the relationship (e.g., biologically effective dose), there is an increased need to test assumptions and hypotheses, evaluate misclassification, and identify and control confounding factors. That is because it is difficult to define the central markers in terms of either exposure or health effect when so many confounding factors (e.g., kinetics, medical history, and rates of transition) can affect the pathognomonic relationships.

Validation and Selection of Biological Markers

The validity of a biological marker for environmental studies should be determined on the basis of the fundamental criteria reviewed by Perera (1987) and discussed below.

Exposure Assessment

There must be a clear hypothesis or model of exposure-response relationships defining the role of the specific marker in relation to the possible exposure scenario. The relevance of markers of exposure is generally easier to establish than that of effect markers when assessing exposure. Relating markers of early biological effect to an original causative agent and routes of exposure is much more difficult, requiring extensive validation studies with careful linkage of an exposure to a marker of effect.

Understanding of Pharmacokinetics and Temporal Relevance

The proper selection and use of biological markers depend on an understanding of the underlying pharmacokinetics and pharmacodynamics of suspected contaminants (WHO, 1986; Andersen, 1987; Smith, 1987; Yager, 1988). Knowledge of pharmacokinetics is important in determining the frequency and timing of sampling and the tissues or fluids most appropriate for study. It also

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guides the interpretation of dose and effect data obtained in a target tissue or a surrogate.

The temporal relationship of markers to external exposure or to disease end points must be clear. Whether an exposure marker reflects recent or cumulative exposures, or peaks or averages, depends on the pharmacokinetics of the contaminant, the persistence of the marker in the biological sample being assayed (which is in large part a function of the turnover rate or half-life of the sample), and repair rates.

Understanding of temporal relevance is essential for developing monitoring strategies and interpreting results. Most measures of internal dose, for example, reflect recent exposures. An exception would be a substance that is fat-soluble and is stored in adipose tissue. Hemoglobin is a good integrating dosimeter over the 4-month half-life of erythrocytes, which, unlike white blood cells, lack repair systems. Human serum albumin has a half-life of 20-25 days. Albumin is synthesized in the liver, where many carcinogens are metabolically activated, so it might reveal adducts not detected in hemoglobin.

The period reflected by white blood cells or lymphocytes is considerably more complex (Perera, 1987; Carrano and Natarajan, 1988). For example, adducts on DNA from white cells can reflect both past and current exposures, because a subset (T cells) is very long-lived. A review of white-cell subpopulations shows that measurements of DNA adducts in these cells will be influenced by the longer-lived T cells and will therefore reflect exposures that occurred both recently and several decades in the past. T cells make up approximately 60-90% of lymphocytes, which in turn constitute about 22-28% of peripheral white cells in circulating blood. Thus, T cells constitute a maximum of 25% of white cells. The estimated half-life of T cells is 3 years. In contrast, B cells and monocytes constitute roughly 1-2% and 1-7%, respectively, of circulating white cells and have lifetimes ranging from days to weeks. Granulocytes make up the remaining 66-85% of white cells and are short-lived (hours to days). Thus, one should consider DNA adducts only in cells damaged while in circulation and not white-cell adducts in circulating white cells, which might result from damage to stem or precursor cells in the bone marrow. When all DNA from a sample of peripheral blood is assayed for DNA adducts, one sees that the long-lived T cells are the major contributor in cases of past discontinued exposure, largely because of their lifetime, which is 100-1,000 times longer. In addition, lymphocytes have lower repair activity than do cycling cells, so DNA lesions are likely to be more persistent in lymphocytes. In cases of current, recent, or long-term uninterrupted exposure to carcinogens, T cells will contribute less importantly to total adducts. The preponderance of adducts will be measured in the shorter-lived granulocytes, B cells, and monocytes.

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In retrospective case-control studies, for example, one would want a permanent marker left decades earlier by an initiating carcinogen. In the case of discontinued exposures, even the longest-lived markers will be diluted by cell turnover, thereby leading to underestimation of past or cumulative dose. Only if exposure had been continuous and had not changed substantially over the decades (and only if the disease had not altered metabolism) would current measurements of the marker be directly representative of critical prior exposure. At the very least, however, such markers as adducts reflect a person's responsiveness to carcinogenic exposures, provided that metabolism was unchanged by disease. Many other exposure patterns are relevant to case-control and cohort studies (current but interrupted, continuous but of varying magnitude, etc.). Each pattern would lead to a different distribution of adducts among white-cell populations and hence to a varied pattern of persistence.

Understanding of "Background" Variability and Confounding Variables

It is essential to know the range of values of a given biological marker in a "normal" population. Care must be taken not to be deceived by the extensive variation in biochemical individuality; what is considered "healthy" in some might indicate a health risk in others (Schulte, 1987). The range of "normal" can be large. For example, it is well known that cholinesterase activity in people not exposed to organophosphorus insecticides covers a wide range (WHO, 1975).

Interindividual variation and intraindividual variation are important contributors to "noise" or background in monitoring or epidemiological studies and should be characterized before large-scale application of a particular biological marker. Such data, however, can be generated only by large-scale surveys with repeated sampling and efforts to control for confounding variables. Thus, a background study is an important exposure-assessment exercise in itself. With respect to carcinogen-DNA and carcinogen-protein adducts, substantial interindividual variation and intraindividual variation have been observed with PAHs, 4-ABP, and nitrosamines (Harris et al., 1985; Umbenhauer et al., 1985; Bryant et al., 1987; Perera, 1987). SCEs also vary widely within and between subjects (Carrano and Natarajan, 1988).

As discussed earlier, biological markers are subject to greater variability than conventional exposure-assessment techniques, because the body actively participates in the collection, distribution, and elimination of absorbed contaminants. Confounding variables that must be accounted for in studies that

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use biological markers include age, sex, race, cigarette smoking, alcohol consumption, diet, drugs or other environmental exposures, genetic factors, and pre-existing health impairment. In fact, it is known that alcohol intake is the most common cause of reduced metabolism of industrial chemicals (Fiserova-Bergerova, 1987). Thus, in a study of those chemicals in which the chemical or a metabolite is used as a biological marker of dose, one would have to account for alcohol consumption if one were to understand and interpret the data properly.

Most reports of cytogenetic studies have given no information on the impact of smoking and other exposures to carcinogens or mutagens on their results. Life-style factors (e.g., smoking and diet) and other chemical exposures (e.g., environmental, recreational, and therapeutic) are also potential confounding factors with respect to SCEs and most other markers. Additional potential confounders are host factors (e.g., health and immune status) and exposures that influence the marker of interest. In a study of PAH-DNA adducts in workers, for example, it is necessary to account for all other background exposures to PAHs and, ideally, for factors that could induce or inhibit metabolism and binding. Those inducers include cigarette smoke, char-broiled meat, alcohol, sedatives, and PCBs; the inhibitors include methylxanthines in foods, steroids, solvents, and spray paints. Thus, even pilot studies attempting to evaluate biological markers can become complex epidemiological exercises that involve careful interviewing.

Reproducibility, Sensitivity, and Specificity

Chemical specificity is a prime criterion for marker selection. Markers should be chemical-specific or at least highly correlated with the contaminant exposure of concern. That is important if effective mitigating steps are to be taken to prevent later exposures.

In addition to being specific, markers should also be "sensitive" to the agents involved in the exposures, detecting a high percentage of persons in the exposed group. Given interindividual variation, not all exposed persons would be expected to be positive; but it is important that the method for assaying a marker be sensitive enough to determine background, so that a true comparison of the exposed and unexposed can be made. Another criterion for sensitivity might be biological relevance. Some postlabeling techniques are able to detect progressively lower numbers of adducts, so a point might well be reached where adducts are of no phenotypic significance. That point could be determined in animal carcinogenicity studies (Ashby, 1988).

Assays should be reproducible, with limited variability ascribable to labora-

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tory personnel or the assay method itself (Gann et al., 1985). Reproducibility includes interlaboratory and intralaboratory reproducibility. When it is possible, different methods for assaying a given marker are useful for detecting artifacts in a method. An example of such a process is the cross-validation of various DNA-adduct marker techniques with immunoassays, ^{32}P-postlabeling and GC-MS, such as that carried out on PAH adducts of Finnish foundry workers.

Feasibility

The biological sample to be assayed must be readily available in humans so that procedures cause minimal discomfort to the participant. Often, understanding of the pharmacokinetics can assist in determining which tissue is most appropriate for sampling.

Assays must be cost-effective. Most assays are still in the experimental stage and cost about $300-500/sample. If multiple assays are performed in tandem on the same biological samples, costs of a study are greatly reduced. That is also the case if stored samples from a prospective study or biological specimen banks are available.

Storage of samples must not allow degradation of the relevant marker. Preparation and assay of samples are generally time-consuming, because repeat assays are needed to ensure reproducibility, but an assay should not require unusually complicated processing or storage efforts.

Study Design

Adequate Sample Size

Sample size is determined by the expected differences in marker frequency or concentration between comparison groups, by the anticipated background in the exposed group, and by variability in measurement data. Considerable groundwork is required to establish those characteristics.

Appropriate Control Populations

Ideally, depending on the type of study (e.g., cohort vs. case-control), controls must be selected from persons expected to be nonexposed. However, in most studies of environmental exposures, there are numerous and often im-

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portant background sources. For example, when one is evaluating inhalation exposure of PAH, ethylene oxide, or styrene from industrial sources, background exposures could include cigarette smoke, diet, and indoor-air pollution. It is necessary to control and analyze for potentially confounding sources of exposure. The definition of the nonexposed group will be the results of analysis of the chemical and biological markers. In many instances, assays have detected a substantial background of industrial compounds in nonindustrial persons, owing to the domestic use or misuse of the compounds. Hence, it may not always be necessary to be marker-free at the beginning of a longitudinal cohort study; however, they should have similar frequencies in each group.

Control of Potential Confounding Variables

This issue has been discussed above. Adequate control necessitates eliciting detailed environmental histories from study subjects. Where it is possible, an array of biological markers should be used to quantify their relationship to the exposure of interest, confirm the validity of the markers, and attempt to detect artifacts. Biological markers of susceptibility are useful to document the presence of confounding conditions.

Use of Batteries of Biological Markers

As noted previously, combination of markers is necessary to account for confounding factors. Multiple markers should also be used to distinguish between recent and earlier exposures. A battery of markers designed to assess the role of occupational exposure to aromatic amines in bladder cancer, for example, might include breathing-zone monitoring for the amines, immunoassays of specific aromatic amine-DNA adducts in white cells (lifetimes of days to years), and cytogenetic effects in T cells (half-life, 3 years). Cotinine in plasma could be used to learn about cigarette-smoke exposure, a potential confounding variable for bladder cancer.

Analysis

For a detailed discussion of the analytical considerations in biological-marker studies, the reader is referred to Thompson (1983), Sheldon et al. (1986), Schulte (1987, 1989), and Margolin (1988).

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ETHICAL ISSUES

The availability of highly sensitive assays that can identify dose and effects resulting from the interplay between low-level exposures and genetic or acquired susceptibility raises several thorny ethical and moral questions. The reader is referred to Ashford (1986), Committee on Biological Markers of the National Research Council (1987), Schulte (1987), and Weiss (1989) for discussion of those issues. Primary among them is the use that is to be made of biological-marker information. Take, for example, the theoretical case of a biological marker known to reflect susceptibility. Should a worker who tests positive or has an increased measurement be removed from the workplace? If so, should he or she be offered an equivalent job in the same industry? Or should the workplace be cleaned up to protect the most sensitive worker?

In reality, few, if any, biological markers are established as predictors of individual risk associated with inborn traits, exposure, or a combination of the two. Therefore, it is important to inform research-study participants in advance that the results are interpretable only on the group level. Participants in such studies should be provided test results that are presented and discussed in context with available information (or lack thereof) on the variability within and between people in the normal (nonexposed) population, as well as that observed in the research-study group.

SUMMARY

Biological markers can be divided into three broad classes: markers of exposure, markers of effects, and markers of susceptibility. The committee focused on the application of biological markers to assessment of exposure to contaminants rather than their use to predict health effects. Markers provide information on dose that can be related to exposure using pharmacokinetic or pharmacodynamic models. However, these markers integrate all routes of exposure, and the actual routes cannot be detected without personal or microenvironmental exposure information. Biological markers, therefore, are best used in conjunction with conventional measures of exposure.

Biological markers range from measures of the intact original contaminant to measures of adverse health effects caused by that contaminant. Relating a marker directly to an exposure becomes more uncertain as measurements are obtained within the progression toward an effect, because the variability associated with the human "receptor" increases along that progression.

Properly measured, biological markers can reduce misclassification errors of degree of exposure and can increase the power of epidemiological studies

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to identify associations between exposure and disease. Markers can, in theory, be useful in developing and validating pharmacokinetic models aimed at relating exposure to dose. They have the potential to improve risk extrapolation between species and between populations and to allow better predictions of human risk. Markers can provide an early warning of hazard or potential risk of disease. Markers measured in stored specimen banks can allow retrospective determination of whether a particular contaminant was elevated in the general population at an earlier time.

Use of biological markers for assessing exposure has several disadvantages and limitations. A major limitation is that most markers are in the development stage and have not been fully validated or field tested. A key question regarding markers of exposure is what compounds and exposures could have produced a marker of a measured amount in a specific tissue. The variability of markers can present problems in establishing quantitative relationships between exposure and response at low-exposure concentrations. Markers reflect diverse behavioral, biological, and methodological processes. Hence, they can be subject to more confounding influences than are measurements of ambient airborne contaminants. By virtue of their collaborative and interdisciplinary nature, investigations of biological markers are demanding in terms of personnel, cost, and effort to develop understanding among researchers.

Analytical techniques with improved chemical specificity and sensitivity for biologically significant markers are needed to apply to exposure assessments, especially flexible assays that can analyze a number of markers simultaneously or be readily adapted to analyze numerous markers sequentially. For such techniques, validation studies are needed to link conclusively biological markers to putative causative agents.

Better pharmacokinetic data are needed for an increasing range of chemicals. These data are needed to further the development and validation of more sophisticated biological-marker models and to further understanding of how to model multiple metabolism pathways as a function of exposure level.

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5

Survey Research Methods and Exposure Assessment

INTRODUCTION

Survey research has become an integral and routine approach to organizational decisionmaking and scientific estimation. Hardly any product can be marketed or political candidate nominated without survey data on public acceptability. However, the quantity of survey research might have outstripped the scientific quality of survey practice. In many surveys, interviewers with little scientific training do little more than hold conversations with other survey respondents. Such surveys are not likely to maintain the methodological standards that are required for scientific validity. Moreover, when surveys appear expensive and sponsors who must pay for them look for ways to reduce costs, methodological standards are usually among the first factors to be sacrificed. That situation probably characterizes most of the survey research associated with exposure-assessment studies. The committee examined many prominent studies in the field and found notable departures from sound survey practice; even the most sophisticated and laudable efforts toward improving survey quality, such as the standardized Environmental Inventory Questionnaire, contain some problematic survey practices.

Properly designed and conducted survey research can provide the precise population estimates needed for exposure assessment relatively inexpensively. The relevant types of information that can be obtained from surveys for exposure assessment include:

- Percentage of the U.S. population or a specific group or community that uses gas stoves, pesticides, or lives in homes with attached garages.
- Numbers of persons who smoke cigarettes, pump gasoline, or apply pesticides on a particular day.
- Amounts of time per day that people spend outdoors, in automobiles, or in the presence of people who smoke.

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Such types of data on time use or time-activity patterns have become important in exposure-assessment research and are central to this chapter.

The methodological steps in collecting time-activity data and all other data collected by surveys include:

- Choosing samples of persons with random-probability methods from complete and carefully constructed sample frames.
- Selecting the most appropriate mode(s) of data collection—usually face-to-face or telephone interaction or the subjects' own completion of a survey form.
- Reaching a sample of adequate size for statistical analyses.
- Achieving a high response rate from the selected sample.
- Deciding on the most appropriate measurement approach—in exposure assessment, these include personal exposure monitors combined with time-activity diaries (direct), time-activity diaries alone (indirect), and single questions or self-reports (questionnaire).
- Designing survey protocols that are understandable by respondents, usable by interviewers, and appropriate for sample projection.
- Framing specific survey questions in language that is simple, direct, and unambiguous.
- Coding and storing collected information in computer-readable form.
- Analyzing the data with appropriate statistical techniques.
- Deriving statistically valid conclusions from the data.

Specific considerations of coding, analysis, and dissemination of survey data are treated only minimally in this chapter, because those aspects of survey research are familiar and present relatively few problems. What is less familiar and recognized is how much the results of survey studies depend on the quality of collected data, particularly when too little attention has been given the first seven steps listed above. This chapter concentrates on those steps.

The seven methodological steps apply to *all* data involving human populations and not just to activities labeled as surveys. For example, data collected in a laboratory or field study that used an inappropriate or inadequate sample might be given undue weight.

Table 5.1 provides a general outline for the three topics to be addressed in this chapter: sample selection, measurement approach, and questionnaire framing and wording. This chapter focuses on advanced survey methods for exposure assessment and is not a how-to guide to survey research. Several useful textbooks on survey research methods can be recommended for the latter purpose: Warwick and Lininger (1975), Fowler (1984), Converse and Presser (1986), and the more elementary introduction of Bradburn and Sud-

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TABLE 5.1 Methodological Factors in Exposure-Assessment Surveys

Sample selection	Probability versus nonprobability method
	Sample frame (target population)
	Equal sampling versus oversampling of groups
	Response rate
	Sample size and related sampling error (precision)
	Other (e.g., sequential sampling and Bayesian estimation)
Measurement approach	Survey mode (face-to-face, telephone, etc.)
	Direct approach (personal monitor and time-activity diary)
	Indirect approach (time-activity diary alone)
	Questionnaire approach
Questionnaire framing and wording	Open versus closed questions
	Single versus multiple items
	Long versus short questions
	Explicit versus implicit questions
	Aspects of time

man (1988). EPA (1984a,b) has also produced a comprehensive and useful guide for conducting surveys. It would be a mistake, however, to assume that any text can make one a survey-research specialist. The elements of survey research and questionnaire construction are subtle arts, currently aided by little scientific guidance and, even more, by professional experience and wisdom. Even in well-established areas of research, each study and study instrument must be shaped by experienced practitioners to meet the study's unique objectives.

Exposure-assessment survey research presents challenging problems because it is heavily involved with obtaining information about time. Personal exposure to pollutants is cumulative and complicated regarding time, and exposure assessors want to document when an important exposure to a contaminant has occurred. They also want to know the frequency of exposure, its sources, its location, and its contaminant concentrations in air and the

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factors that effect them (e.g., ventilation), the breathing rates and other physiological states of the exposed person, and the general health status of the exposed person. The question "How long and how often was the exposure?" raises some difficult estimation problems. At one extreme, one can look at a very short period, such as an hour or a day; such studies require a high degree of control or precision. At the other extreme, one can look at far longer periods, such as a decade or a lifetime; these entail much less precision or control. Survey researchers can ask how often an individual respondent might have been in a situation that was likely to involve significant exposure, but the respondent's memory of such occasions is extremely problematic. Research on respondent memory has revealed a host of biasing factors and ambiguities (Tulving, 1983; Bradburn, 1987; Pierson et al., in press). Thus, there has been increased interest in the more precise measurement of activity during very short periods, such as the day or the hour, for which the time-activity diary is very promising as a measurement option. Most exposure-assessment studies begin with only a general statement of the issues. To paraphrase a summary from another field:

> Some exposures to some contaminants of some sources for some periods at some frequency and concentration in some environments with some ventilation during some activities at some breathing rates have some health effects on some people.

Such a statement might seem at first glance vague or capricious. But it does show that many variables must be taken into account in estimating exposures and effects. It also shows that a few simple guidelines and checklists will not suffice in exposure assessment. Obtaining necessary information on the temporal and spatial distributions of contaminants of interest and on the population possibly exposed to them requires a highly coordinated multidisciplinary approach. Thus, it is not reasonable to expect a single breakthrough in technique, such as automated diaries or less obtrusive monitors, to address more than part of the overall estimation problems.

Once the variables mentioned earlier are considered in the study design and study participants are identified, the central problem is to ensure that the survey instrument used in the study is completed in an appropriate and understandable manner that will result in useful information.

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SAMPLE SELECTION

The matter of selecting study participants is more straightforward than survey design, but strict guidelines need to be followed. Statistically proper sample selection is crucial for valid and accurate extrapolation from sample characteristics to general-population characteristics. Sample selection procedures for survey research on human behavior have a solid scientific and quantitative basis. The mathematical principles involved are rather simple and straightforward, but often neglected in conducting surveys. Selection of samples should have the following characteristics:

- The selection of individuals within a target population or within a specified period must have a random probability basis. Otherwise, the resulting data will have at best limited generalizability.
- The design of a sample frame involves identifying potential participants and implies series of rules to be followed in selecting individuals in the target population. Each individual must be identified in the frame and have a known chance of selection.
- The selection process should ensure that all individuals in the frame have an equal chance of selection or specify that some individuals of particular interest (e.g., older people, asthmatics, or people in rural areas) have a greater (but known) chance than others of being selected and oversampled.
- The sample frame should make it possible to calculate a response rate, the proportion of sampled individuals who participate in the study (i.e., provide the required data). That is a crucial gauge of the quality of the sample. If a sample frame specifies that 1,000 persons be selected into the sample, but only 200 or 300 actually participate (respond), the response rate is only 20% or 30%. Such a low response rate will raise important questions about the generalizability of the data, particularly if those who do respond can be said to have self-selected themselves into the sample and thus have biased the sample-selection process. Only careful follow-up methodological studies can determine how serious such response-rate problems can be for exposure assessment.
- Assuming that a probability sample has been drawn, that nonresponse bias is negligible, and that measurement error also is negligible, statistical formulas should be used to calculate the sampling error of an estimate based on the sample. Calculated estimates of precision are not appropriate if the response rate is low or if there are substantial measurement errors or problems.

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Target Population

In studying human exposures, it is first necessary to determine whose exposures are to be assessed—i.e., one needs to determine the target population or *sampling frame*. Depending on the goal of a study, one could select from a variety of target populations, e.g., the U.S. national population, persons who reside in a particular community of interest, or persons who satisfy particular eligibility criteria. For epidemiological studies, one might be interested in a susceptible population, such as asthmatics or school-age children. For compliance studies, one might be interested in the general population of a geographic region.

If the target population is small, it might be possible to take a census and measure every individual in the population. Otherwise, one needs to select a sample from the target population and measure the individuals in the sample. Even when the population is small enough for a census, it might be preferable to use a sample and obtain more detailed information from those measured.

It is crucial in selecting the sample to use an appropriate probability sampling method, so that each individual has a known and nonzero chance of being selected. Depending on the goal of the study and the availability of prior information, one could set the sampling probabilities to be equal or unequal. If a specific subpopulation is of interest, one might oversample from that subpopulation, i.e., use higher sampling probabilities for individuals in it. If it is known or believed that the outcome of interest might be more variable in a subpopulation, one might also oversample from that subpopulation. When the goal of the study is to estimate characteristics of an entire population by combining information obtained from subpopulations, the Neyman allocation technique (Cochran, 1963) can be used to designate sample sizes for subpopulations. It is always important that each individual have a nonzero sampling probability, if the sample is to be generalizable to the target population.

Samples not based on probability sampling methods are often used in preliminary stages of exposure assessment. For example, investigators might conduct a pilot study of a new instrument on their colleagues or on volunteers. The results of such measurements might be useful for evaluating the instrument or testing overall field procedures, but the data collected usually cannot be generalized to any wider population. The same is true for studies performed with small or unrepresentative samples.

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Response Rate

If one is to generalize from a sample to a target population, one must obtain a high proportion of responses from those sampled. Low response rate is probably the source of most of the quality problems associated with survey research. The U.S. Census Bureau and other government agencies can often obtain responses from more than 90% of those eligible. Academic research organizations usually have 65-75% response rates. Most commercial firms seem satisfied with 40-50% response rates. In many surveys that receive wide attention (e.g., in the mass media), effective response rates are less than 20%.

Low response rates warrant careful scrutiny, because they raise the possibility of substantial nonresponse bias. If respondents and nonrespondents are different, the data collected on the respondents are of questionable generalizability to the entire target population. Therefore, each survey should include an evaluation of the nature of nonresponse and the presence of nonresponse bias, particularly if the response rate is much less than 70%.

Nonresponse can have a variety of causes, such as failure to locate potential respondents, refusal to participate, inability to provide required information (e.g., due to illiteracy or language problems). Perhaps most importantly, potential respondents' might lack interest in the study or topic. In carefully designed surveys, exact percentages of different types of nonresponse are calculated. Some types are unlikely to be associated with the outcome of interest and therefore do not lead to nonresponse bias. Analysis of the causes of nonresponse is useful for identifying the potential for nonresponse bias and for reducing nonresponse.

A low response rate by itself does not necessarily lead to nonresponse bias, but it suggests a potential for it, especially in studies that make great demands on survey participants. To evaluate the presence of nonresponse bias, one needs to compare respondents and nonrespondents. Several survey devices are available, such as collection of a minimal set of data from a sample of nonrespondents with a short and less burdensome questionnaire, offering of monetary incentives to a sample of nonrespondents to persuade them to participate, and comparisons of groups of respondents, e.g., stragglers versus early respondents.

If nonresponse analysis indicates little or no difference between respondents and nonrespondents, one might assume that nonresponse is random and does not cause nonresponse bias; one can then analyze the observed data directly. However, if respondents and nonrespondents do differ (e.g., if urban residents are more likely to respond than rural residents), it will be necessary to adjust for the difference. Given an adequate amount of background information on respondents' residence locations, demographic characteristics, etc.,

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it might be possible to generalize from the observed sample to the target population with statistical techniques, such as the reweighting or imputation steps presented by Kalton and Kasprzyk (1986). The techniques generally assume that, if nonrespondents have the same background characteristics as respondents, their exposures (and exposure distributions) are the same. The respondents' exposures are thus used to impute the nonrespondents' exposures.

Sampling Error

Statistical formulas can be used to estimate sampling error. Three factors are involved: the variance in the sampling, the sample size, and the sampling rate (the fraction of the entire population that is sampled). The sampling rate usually can be disregarded if the sample comprises less than 10% of the population from which it is drawn. For a simple random sample taken to estimate a specified population proportion (e.g., smokers or persons exposed to a specified contaminant on a particular day), sampling error is calculated according to the following equation:

$$sampling\ error = [(p)(1 - p)/n]^{1/2} \qquad \text{(Eq. 5.1)}$$

where p is the estimated proportion of the population having the characteristic (e.g., smokers) in the sample and n is the sample size. Multiplying the sampling error value by 1.96 and adding and subtracting the result from p gives a rough 95% confidence interval for the sample estimate; multiplying the sampling error value by 2.54 and adding and subtracting the result from p gives a rough 99% confidence interval. If the sample size represents more than 10% of the total population of interest, then the error can be reduced by a factor: $(1 - \text{proportion of population sampled})^{1/2}$. For example, if, in a sample of 600 people, 40% are found to have a characteristic, equation 5.1 leads to an estimated sampling error of 2%. With 99% confidence, the true proportion lies between 35% and 45% (i.e., $40\% \pm (2\% \times 2.54)$). Use of the equation assumes a random sample, no important response-rate anomalies, no clustering of respondents, and no generalization beyond the original population. The above calculation of the confidence interval assumes a normal distribution for the sample estimate. In practice, the assumptions for equation 5.1 are not often met. In such cases, a correction factor is used. For example, for in-home personal interviewing with high clustering of respondents,

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equation 5.1 produces error estimates that are too small and need an appropriate inflation factor.

The size of the sample is important in reducing sampling error, but sample size alone does not ensure sample quality. Determination of a proper sample size depends on the type of inference to be drawn, the sample variance, the degree of precision desired, and the adequacy of the response rate. It is important to note that sampling error varies inversely with the square root of the sample size.

Other Features

Three further features of sample design can increase a survey's effectiveness. Rather than a single large survey, a series of small samples can be drawn sequentially until stability in estimates and inferences is achieved. That can be especially important in personal-monitor studies, which are extremely expensive.

Efficiencies in sampling design also can be achieved by using data from existing time-activity pattern studies (described later). Fairly consistent estimates of time spent outdoors or time spent in travel, for instance, have been published, and the background factors that are associated with larger or smaller portions of time spent in such activities also are fairly predictable (Robinson, 1977; Juster, 1985). For example, day of the week, employment status, and educational level have more to do with time spent away from home than do age, region of the country, or season. That means that well-executed samples of single local areas taken at single times of the year can provide considerable insight into exposure conditions in other locations. In other words, activity patterns in Denver, Cincinnati, and Jackson (Michigan) do not appear that different from each other and closely resemble national patterns of time use.

A third sample-relevant consideration is the use of panel studies that involve multiple periods of observation of the selected respondents. Especially in exposure studies, one needs exposure readings for individuals on more than a day or a week. Following the same individuals across time provides an essential perspective for future exposure-assessment studies.

MEASUREMENT APPROACHES

The process of exposure takes place across time, and exposure assessment needs to be sensitive to the time element in all data collections. Three meas-

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urement approaches can be distinguished in population-based exposure assessment: direct, indirect, and questionnaire. In the direct approach, respondents report in time-use diaries and carry personal exposure monitors that record their exposures for short periods. In the indirect approach, exposure is imputed from the activities that respondents report in time-activity diaries. In the more traditional questionnaire approach, exposure is imputed from responses to self-reported factual questions (e.g., occupation, age of dwelling unit, and fuels used for heating and cooking) or to general questions regarding activities (e.g., frequency of using pesticides). Personal exposure monitors are not used in the indirect approach or the traditional questionnaire approach.

Direct Approach

With the direct approach, human subjects carry personal monitors while they engage in their daily activities. Exposures are thus measured directly and objectively and without the reporting problems associated with questionnaires. However, without some respondent self-report or outside information, there is no way to understand the contaminant pollution sources that led to exposures or the reasons why notable exposures were recorded by a monitor. Therefore, one usually needs detailed activity reports, such as those available from a time-activity diary.

The other major problems that arise in personal-monitor studies result from the cumbersome nature of most personal monitors. The use of cumbersome devices can result in high noncompliance rates. Also, presence of the monitors can reduce the utility of the data that are obtained by affecting the behavior of the respondents. Respondents might be more likely to restrict their activities when they carry equipment. When interacting with other people, subjects might try to conceal the equipment or otherwise wear it improperly. (Such phenomena can also affect the quality of data that respondents provide in related questionnaires.)

Exposure researchers must take particular care not to overburden the subjects when collecting survey data from them in exposure studies. When time-activity data were collected in early exposure studies, such as the TEAM study conducted in the early 1980s in Denver and Washington (e.g., Hartwell et al., 1984; Johnson, 1984), completion of the diary was one of many requirements for the respondents. Sometimes, neither respondents nor interviewers were adequately prepared for the demands and rigors of completing the time-activity diary. As a result, some diaries contained more than 24 hours' worth of activities, others less than 24 hours' worth. Large periods were not accounted for; e.g., some respondents reported no meals or sleep during 24 hours.

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In some diaries, the periods of instruction by interviewers or technicians were recorded as normal daily activity. Activities like child care or shopping were seriously underreported or not reported at all. Nonetheless, the researchers were able to use the diaries to identify certain locations (e.g., parking garages) or activities that involved maximal exposure. The estimates of time that respondents spent in those locations might have been flawed, but the personal exposure data could be merged with more carefully designed and conducted time-activity studies.

Indirect Approach

The indirect approach does not involve the problems and expenses associated with using personal monitors. Instead, one separately measures the activity patterns of a sample of human subjects and merges the data with data on contaminant concentrations found in independent samples of microenvironments (e.g., from fixed-site monitoring) to assess exposure. The main advantage of the indirect approach is that it places less burden on respondents than personal monitoring and is thus able to achieve higher response rates.

Time-activity data can be obtained with several procedures, such as estimation by respondents in the study sample, by direct observation, or from time-activity diaries. In the estimation approach, people are asked to estimate the amount of time they spent in various activities during a given period, such as the previous year or the previous week. This is usually the least burdensome technique, although its reliability and validity are unknown and highly subject to the frailties of human memory and understanding.

In the observational approach, respondents' activities are monitored by outside observers. That adds a valuable degree of realism and completeness to the data collection, but the presence of an observer is likely to influence a respondent's activities. It is also likely to entail high rates of refusal to participate in a study.

Time-activity diaries have the greatest potential utility of the three indirect approaches. Respondents are asked to described sequentially all the activities in which they engage during a given period, usually a day or a week. The diary can be filled out concurrently with participation in the activities as in the Total Human Environmental Exposure Study (THEES) (Lioy et al., 1988), in which respondents were instructed to record all their activities for a 24-hour period. It can also be done by recall, as in the California Air Resources Board (CARB) Activity Study, in which respondents were asked to recall sequentially all their activities of the previous day. More burdensome for respondents than simple estimation, diaries provide a far more informative

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and comprehensive account of daily activities. The reliability and validity of data from diaries have been encouraging when tested against independent measurements (Robinson, 1977, 1985; Juster, 1985).

Most diary studies have been for sociological purposes, not for pollution estimation or environmental research. For exposure-assessment purposes, that means that crucial activities, such as smoking and working with engines or solvents, are not distinguished in the coded data. An important exception is the current statewide study being conducted by CARB. The CARB study was designed specifically for exposure assessment, and it measures periods of exposure to environmental tobacco smoke, time spent in specific rooms in the home, and occurrences of exposure to solvents and other pollutants (Robinson et al., 1989). The estimates generated from the study represent important advances in obtaining more refined and detailed estimates of specific exposures.

Methodological research has indicated that time-activity diary data are generally reliable and valid, although more definitive validity work should be undertaken. The use of time-activity diaries has several advantages over other ways of measuring time spent in activities:

- It is complete, in that respondents are asked to report on all their activities over a full 24-hour period.
- It is natural, in the sense that it resembles the way most people seem to organize, store, and retrieve information on their daily activities.
- It relies less on respondents' recall ability by concentrating attention on a single day or week, rather than asking respondents to provide hypothetical estimates of their usual activities or of their cumulative hours or minutes over longer periods (which vary by day of the week or season and thus can be very difficult to estimate).
- It can indicate unanticipated changes in the trends of activity patterns because it uses the 24-hour "zero sum" property of time: all activities must sum to 24 hours. Thus, if time is spent on some new activity, it occurs at the expense of other activity. It is therefore possible to identify tradeoffs in activities across time; e.g., what changes occur in people's activities if they spend more time playing sports or less time cooking.
- The use of open-end activity descriptions (i.e., in the respondent's own words) in the diary makes it possible to recombine or recode activities to fit different objectives of an investigation. This has become streamlined with the development of computer-assisted telephone interview (CATI) programs to record time-activity information, as in the CARB study (Robinson et al., 1989).

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The diary makes it possible to extend traditional census demographic techniques and population counts to portray human activity with a time dimension and that makes it possible to approximate a census of behavior or activity in society on a person-day basis. In such an activity census, the person-day framework allows extrapolation to the population at large. One can estimate with some precision how much time a target population spends working on automobiles, going to the dry cleaners, cooking meals, and, at least theoretically, any other activity that takes place. Of more concern is the possibility of estimating time spent in microenvironments, such as outdoors in transit or at home, etc. The work of Chapin (1974) showed how this research can be extended to include spatial coordinates of activity and thus give a fully spatial-temporal set of activity accounts.

Results of several national time-diary studies conducted with the general approach (e.g., Szalai, 1972; Robinson, 1977; Juster, 1985) provide a basis for national estimates of time spent in specific environments and activities and of the times of day for specific activities and locations. They also indicate that some important changes in activity are taking place, such as the time that women are now spending away from home, or the increased proportion of at-home time they spent watching television (Gershuny and Robinson, 1988).

Some aspects of time use important for environmental research are missing from national time-diary collections. Some of the missing elements are these:

- Differentiation of key microenvironments, which are coded crudely. For example, time at home is not differentiated by room in the home.
- Specification of potential high-pollution microenvironments (like parking garages, dry cleaners, and auto repair shops). Time spent in those locations cannot be separated from time spent in low-pollution environments.
- Breathing rates during activities. Because few people can describe their exact breathing rates, they must be estimated from type of activity.
- Other ambient conditions during activities (e.g., presence of smokers or open windows).
- Distance from important potential pollution sources (e.g., gas ovens and pesticides).
- Information on the general structure of the home or workplace (number of rooms, presence of an attached garage, open spaces, etc.).
- Health status of respondent (e.g., asthma and handicaps).
- Information about children (under the age of 18).

The most recent national data, collected in 1985 (Gershuny and Robinson, 1988), are available for only a single day, so long periods of exposure cannot be estimated for most of the population. That is especially important for

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segments of the population who might be at risk from cumulative multiple exposures.

Thus, although some available national data are useful for general activity-estimation purposes, important gaps in detail greatly limit their value for modeling population exposures. The time-activity data usually need to be integrated with specific independent data on airborne chemicals or biological markers or their surrogates. That was a main reason behind the CARB decision to adopt the basic time-activity diary method for environmental-exposure estimation (Robinson et al., 1989). In particular, the CARB studies of 1987-1989 included the following measurement features:

- A detailed location code that differentiated rooms in the home.
- Fine-grained activity codes stored in original verbatim format from respondents and coded into more than 100 categories.
- Information on exposure to several possible pollution sources (e.g., gasoline engines and pesticides).
- Information on exposures in the workplace.
- Information on passive exposure to tobacco smoke for each activity throughout the day.
- Information on the daily activities of children, especially those under 12.

As detailed and focused as the CARB survey was for exposure research, it did not include information on the general health status of the respondents, their exact distances from possible pollutants, their breathing rates during activities, or open spaces in their workplaces or home. Moreover, the activity analyses were confined to a single day for each respondent. Utility for predicting or estimating exposures over longer periods, such as a week or a month, is unknown.

The 1975 University of Michigan time-diary study (Juster, 1985) did collect information on 4 days (2 weekdays and 2 weekend days to provide estimates of a "synthetic" week's activities), but the days were scattered across the year. Even though only a minority of respondents in this study described their single diary day as "typical," there was considerable predictability of activities from one day to the next, especially across weekdays (Kalton, 1985). Estimation of longer-term cumulative activities of individuals from single-day diaries is problematic, and a useful goal of future research would be to identify the level of predictability by collecting diary data across a full week. That has been done in England, although the response rates were less than 50% (Gershuny et al., 1986).

Even a week might be too short a period for detecting cumulative exposures to many pollutants. Until some kind of prospective panel study can be

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Source: https://www.industrydocuments.ucsf.edu/docs/zxxj0001

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arranged in which respondents agree to keep accounts of their activities and likely exposure for a month or a year, the only option is to obtain data with questionnaires, which incur the many problems associated with respondent memory. Obtaining long-term, multiple-day diary information from a representative sample of respondents remains a major subject of needed research—particularly with respect to cumulative risks for various pollutants.

The measurement of activity patterns can be seen to involve the five elements who, what, where, when, and why:

- Who is in the target population and the sampling frame?
- What are people doing at various times of the day?
- Where do the activities take place (such as outdoors and in automobiles)?
- When and for how long, during the day or year, do activities take place?
- Why do activities take place?

The detail of activity-pattern measurement depends on the goals of a study and the contaminants being studied. For general-purpose studies such as the TEAM study that deal with a wide variety of contaminants, coarse descriptions of activities (such as indoor vs. outdoor or smokers present or absent) might be sufficient. For studies, such as THEES, that are focused on a specific pollutant, more information is needed on the sources of contaminants and the types of situations in which large exposures can occur, especially activities (like cooking and bathing) that could generate particular pollutants. The time of contact with contaminants also needs to be estimated accurately. Daytime outdoor exposures might be considered different from evening outdoor exposures for pollutants, such as ozone, that have diurnal cycles.

For some microenvironments—such as homes, shops, and offices—standard probability sampling methods (e.g., use of area probability samples) can be readily applied. For other microenvironments, such as automobile trips, appropriate sampling techniques are less obvious and need to be developed.

Integrating Personal-Monitor and Diary Information

Time-activity diary information should provide a better understanding of exposure and predictions of exposures based on personal-monitoring studies. Ideally, of course, one would like to have continuous activity and air-contaminant monitoring, so that one could identify activities or locations in which peak exposures occur. With passive air-contaminant monitors, however, that

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task becomes much more difficult, because the time of episodes of peak or unusual exposure cannot be identified. Personal-monitor studies raise sampling problems in addition to time-specification issues. If monitors are not worn at a respondent's breathing height, for example, measured concentrations of contaminants might be higher or lower than those to which the respondent is actually exposed. A respondent with a small passive monitor might cover it with an overcoat or sweater to conceal it or to keep warm.

Time-activity data from representative diary studies can be used to calibrate or adjust personal-monitor data that are unrepresentative with respect to the samples of people who cooperate or activity patterns that were affected by the very presence of monitors. Data from time-activity diary studies can be used as benchmarks to reveal whether special high-risk groups deviate from the rest of the population in activity patterns (e.g., by spending more time in bars, dry-cleaning establishments, or gasoline stations). Diary data can be used to identify population groups whose activity patterns can lead to large exposures and to identify their special demographic features (e.g., younger people or urban residents). As noted in Chapters 2 and 6, time-activity data can be used in modeling general activity or exposure within various microenvironments. Diary data might be less useful for modeling pollutant effects that are difficult to detect over short periods, such as a day or a week. The data can be used to identify high-risk and low-risk populations, without further specification of such factors as sources of pollution, distance from sources, or ventilation and dispersion factors. To be optimally used for such purposes, more detailed diary data, along the lines described earlier, are needed.

A well-designed set of traditional questionnaire items might help to identify high-risk populations and to predict exposure. They could include estimated frequency of exposure to tobacco smoke, gas ovens in enclosed areas, and distance from those exposure sources. In general, time-diary studies do not indicate large variations in activity or location patterns by such basic variables as marital status, presence of children, region of the country, or season by themselves. But season, age, and day of the week can make a difference in the likelihood of going to work. Going to work outside the home usually implies a change in activity patterns and location. Sex, level of education, and health status (and less critically, income) are important factors and should be included and controlled for in future monitor studies. The responses to such questions should be validated and calibrated with time-activity diary information.

As mentioned previously, time-activity patterns at a single location (e.g., Jackson, Michigan) appear to resemble national patterns closely. The general consistency of time-activity data across geographic areas in practical terms means that one can gain generalizable insight from personal monitor and diary

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studies conducted at single times of the year in single communities, provided that samples are drawn randomly, so that all segments of the community are represented equally or in proportion to their risk of exposure.

Questionnaire Approach

Almost all studies depend on some kind of traditional questionnaire to identify the background of respondents through factual information, such as their ages, occupations, general life styles, and access to household technology. The framing and wording of any questionnaire have a great effect on the responses to it and the inferences that are drawn from them. In general, the more standardized the question, the better it is for supporting inferences across studies.

The development of the Environmental Inventory Questionnaire (EIQ) (Lebowitz et al., 1989b) constitutes an excellent beginning in improving the quality of questionnaires for exposure- assessment research. It contains seven items on geographic location, eight on housing, nine dealing with occupation and family members, two on smoking in the home, six on home appliances, six related to radon, and six related to organic pollutants.

EIQ's strengths might lie more in the variables that it defines than in its specific question framing wording. Perhaps that is best illustrated by the questions related to estimated exposure episodes. In the case of tobacco smoke, for example, questions are asked about the amount of smoking in the home on the "most recent weekday" and "most recent weekend day." If interviews and smoking are distributed evenly across the week, that means that Sundays have six times as many chances to be selected as Saturdays, and Fridays three times as many chances as each of the other weekdays. If the family was away one day, estimated exposure will be underrepresented.

In the case of heating sources, the EIQ asks about the use of gas ranges, space heaters, etc., "during cold weather" and "during the winter." Those obviously are subjective terms with no clear referent period. The questions should specify months or temperatures. The response alternatives for some questions include "3+ days a week", "1-2 days a week", and "only in the morning to take the chill off (less than 1 hour)." Those scale inequities (days vs. hours) make it difficult for respondents to answer precisely. Similarly, questions about use of pesticides and herbicides outdoors refer only to episodes longer than 1 hour over the previous 6 months, whereas shorter duration or frequency of use need to be considered as well.

Finally, the EIQ asks a number of factual questions about number of rooms and construction materials. Those seem straightforward at first, but

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might be difficult for less-handy respondents or renters—who probably make up a majority of the population—to answer. Even the number of rooms in a house might not be clear. Year of construction and number of stories could entail difficulty for recent occupants (if roughly 20% of Americans move every year). Such terms as "attached carport" and "closed completely" are susceptible to misunderstanding. Questions that ask only about the fuel used most often miss important details.

Even though the EIQ is a laudable advance in data-collection methods, its questions need to be adapted to and modified for particular study purposes—this could be done most effectively by persons trained in survey techniques.

Factual Questions

When contaminant-concentration measurements are not possible, factual questions can be asked to indicate the presence of exposure-related events or situations. For example, one might ask respondents whether they have been exposed to specific potential pollution sources, such as smokers, gasoline engines, and paints.

Although it does not provide much quantitative information, the factual approach can be a useful screening device for revealing the presence of excess exposure. Answers to factual questions can identify smokers or people whose occupations put them at high risk. The exposure models discussed in Chapter 6 usually require data on factual features of a person's life that can also be considered surrogate measurements, such as occupation, year of construction of residence, types of fuel used for heating and cooking, and presence of attached garages. Those types of questions were developed for the EIQ.

QUESTIONNAIRE FRAMING AND WORDING

Questionnaire results are subject to measurement error in the same way as physical and chemical measurements based on personal monitors. Both questionnaires and monitors can produce readings that differ from the actual value of the characteristic being measured. But a main advantage of exposure data obtained from monitors is the avoidance of many problems inherent in asking respondents questions.

The sources of problems that arise in asking questions are endless, and there are few solid scientific guidelines for framing and wording questions. However, a substantial body of research literature and experience has developed in the field of survey research, and recent studies have addressed the

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issues with the method known as the split ballot (e.g., Schuman and Presser, 1981; Bishop et al., 1982). In this method, one randomly chosen half of a sample group is asked a question in one form and the other half in another form. Unfortunately for exposure assessment, most of the experimental studies have involved questions of opinion, rather than behavior, and there is minimal translation of different ways of asking opinion questions to ways of asking factual and behavior questions. How one resolves inconsistencies when two forms of a factual question produce different results remains a problem. Some form of validation will eventually be needed, through either direct observation, dual measurements, triangulation, or other techniques.

To illustrate the reporting problems encountered with straightforward factual questions, we can consider respondents' reports of whether their homes had basements. Between two periods in one panel study, roughly a 10% inconsistency rate was reported; that is, there was only 90% agreement from one time to another regarding the presence of a basement in the home (Beveridge, 1983). Because any change implies that people either filled in their existing basements or dug out new basements between the study periods, a 10% difference must be a reporting error—on a factual matter that should be readily observable and reportable. This example provides a sobering perspective on the ability of survey respondents to report accurately on their own behavior or circumstances. However, responses to time-estimate questions will more likely reflect potential exposure if an activity is more regular or repetitive (e.g., commuting to work versus taking clothes to the dry cleaners).

Because a simple decision to word a question one way or another can result in discrepant estimates, it is necessary to conduct split-ballot experiments to identify the magnitude of discrepancies or measurement error. To illustrate more options that are available, we discuss five below:

- Open-end versus closed-end questions.
- Single versus multiple questions.
- Long versus short questions.
- Explicit versus implicit questions.
- Long versus short reporting periods.

In contrast with closed-end questions, open-end questions yield responses that are in respondents' own words, provide insights into respondents' frame of reference regarding the questions, are more detailed, and minimize the frames of reference imposed by the researcher. Closed-end questions have the advantages of ease of administration, ease of coding, unambiguity of response, and lower costs. Cost factors invariably favor closed-end questions, which offer respondents no opportunity to describe situations in their own

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words. Time-activity diary studies, in which respondents describe activities in their own words, provide a much richer and more widely useful data base than studies in which interviewers enter activity information into a limited number of precoded categories. The open-end approach has been a feature of national time-diary studies and the TEAM study; the closed-end approach has been used by Spengler et al. (1985), Lioy (1988), and Leaderer (1990a).

In general, it is assumed that a series of questions provides more complete data than a single question, because a series reminds respondents of instances that they might not otherwise have considered. In exposure research, rather than asking respondents whether they generally use detergents, one could read them a list of the names of the most popular detergents as part of a question series.

Much the same issues arise with regard to question length. In general, the conventional belief has been that shorter questions are better, because they are easier to follow, are less ambiguous, and involve less time (cost) to ask than longer questions. That view is now being reconsidered in light of research showing some benefits of longer questions. Like series of questions, longer questions tend to remind respondents of instances they might not otherwise have considered. Although longer questions can change the level of response, responses might show the same pattern of correlations with age, occupational status, emission source, etc., as shorter questions.

It is usually preferable to ask respondents explicit questions, rather than expect them to retrieve information from memory in response to implicit questions. For example, it is considered easier for respondents to answer the question "Were you in the company of anyone who smoked yesterday?" than the question "Are you in the company of smokers often, sometimes, or never?" Implicit terms like "often" mean different things to different respondents and require more inference, whereas "yesterday" should have the same meaning to all respondents. Similarly, in the case of long versus short reporting periods, one should expect more accurate reporting about short and recent periods (e.g., yesterday or last week) than about long or more distant periods. Nevertheless, experimental data are needed to substantiate the expectation or to calibrate for corrections.

Throughout the process of question development and evaluation, one needs to ensure that questions are tailored as closely as possible to respondents' abilities and willingness to answer. Multiple pilot tests with respondent debriefings or analyses of taped interviews are to be encouraged. Results of split-ballot experiments provide the most persuasive case for asking a question one way rather than another.

Because there is no best way to ask a question, a realistic approach is to consider all questions as having their imperfections and problems that require

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researchers' attention. Moreover, what might improve a question on one criterion might not on another.

No questionnaire can eliminate measurement error entirely. Although it is important to estimate the magnitude of measurement error for a questionnaire, such estimation does not appear to be a common feature of survey questionnaires. In some situations, it might be possible to validate respondents' answers directly. For example, after a telephone interview, interviewers might visit a selected sample of respondents' homes to verify the presence of a basement or a type of insulation. When direct validation is not possible, repeated measurements can be used to estimate the reliability of responses. But reliability does not address the problem of systematic errors or bias: respondents might well report the same mistake, no matter how the question is framed.

IMPROVING SURVEY QUESTIONS

There is a major need to develop reliable and valid questions for exposure-assessment research. Failure to appreciate many elementary principles of question format and design is evident in questionnaires done to date, even the praiseworthy EIQ. Building on the results of methodological studies and more refined time-activity diary studies, one should be able to develop a concise inventory of exposure-related questions for a variety of contaminants to identify populations at risk. That should be done in conjunction with personal-monitoring studies, in which both short-term (diary) and long-term (estimate) questions could be asked of the same respondents. How well can one predict cumulative exposure (as measured by a monitor) from the time-activity diary and the estimate questions? Both diary and estimate questions would need to be tailored to capture aspects of exposure not examined extensively to date (e.g., breathing rates, distance to source, and ventilation). The advantages of a panel-study design, involving multiple periods of observation of selected respondents, are especially evident, in that long-term behaviors and effects can be assessed or modeled.

The committee proposes the following guidelines on question wording:

- Questions with precise time frames (e.g., "2 days per week" or "10 times per year") are clearer to respondents and give more consistent results than questions with imprecise time frames (e.g., "often" or "most of the time").
- The narrower the time frame (e.g., "2 hours per week," rather than "3 days per week"), the clearer the question is to respondents and probably the more consistent the results.

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- Estimate tasks should be broken into manageable subtasks (e.g., if "hours per week" is desired, ask for daily estimates for each day of the week).
- Where possible, respondents' time estimates should be forced to sum to a specified total (e.g., 168 hours a week or 52 weeks a year) to increase accuracy survey and comparability across respondents.
- Multiple-scale responses clarify a respondent's task (e.g., "about 3 hours per day *or* about 21 hours a week").
- Memory aids can be useful for specific activities, microenvironments, or contaminant sources (e.g., it is sometimes useful to ask respondents to recall the most recent occurrence of the phenomenon of interest).

Throughout, one needs to recognize that survey respondents' concern over and attention to issues are far lower than those of professional researchers. Therefore the researcher must help the respondent to understand the reasons for the questions and the type of information being sought.

Although researchers should be wary of the lack of precision in respondents' estimates, such estimates can be very useful for relative measurement purposes. For instance, people who estimate that they use pesticides 10-19 days per year might report more related health effects than those who estimate pesticide use at less than 10 days per year—and both groups might show less effect than those who estimate 20-29 days per year. Similarly, those who have worked in high-exposure occupations for 5-9 years might report more related effects than those who have worked in such occupations for less than 5 years. Of course, there is no guarantee that such monotonic relations will be found, and the extent of such statistical correlations needs to be empirically documented.

INCORPORATING SURVEY-RESEARCH METHODS INTO EXPOSURE ASSESSMENT

Exposure assessment should enlist the expertise of multidisciplinary teams of specialists including survey statisticians and field specialists. Many assessments are being conducted independently by investigators whose interests are restricted to single subjects, such as modeling, monitoring, or time-activity estimation. As a result, current exposure studies are unnecessarily restricted to laboratory studies, epidemiological analyses, personal-monitor studies, or national surveys. Specialists need to increase their communication with one another if more-integrated exposure assessments are to be designed and conducted.

Exposure research would benefit from the involvement of survey statisti-

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cians and field specialists, who could help to reduce survey-related errors and the wide variations in survey responses observed in present studies. There seems to be little recognition of the need for probability samples or high response rates, which are as important in small studies as in large ones. A series of small benchmark surveys of normal activity patterns or microenvironments would help to establish a basis for comparison in future exposure assessments by, for instance, defining healthy buildings for studies of the sick-building syndrome.

Application of survey-research methods can also contribute to improving the effectiveness of exposure-study design. It can help to identify the contaminants and microenvironments likely to result in the most important health or nuisance effects. It can also help exposure assessments to target study efforts on chronic or peak exposures on a basis consistent with the biological response time of the contaminant of concern.

SUMMARY

Exposure assessment presents challenging problems for survey research applications because of its intimate involvement with obtaining information about time. Personal exposure to pollutants is cumulative and complicated regarding time, and exposure assessors want to document when an important exposure to a contaminant has occurred. They also want to know the frequency of exposure, its sources, its locations, and its contaminant concentrations in air and the factors that affect them, the breathing rates and other physiological states of the exposed person, and the general health status of the exposed person.

Survey researchers can ask how often an individual respondent might have been in a situation that was likely to involve significant exposure, but the respondent's memory of such occasions is problematic. Thus, interest has increased in more precise measurement of activity during very short periods, such as the day or the hour, for which the time-activity diary is promising as a measurement option. Sample selection, measurement approach, and questionnaire framing and wording are the general aspects considered in this chapter for collecting time-activity data and all other data collected by surveys.

Statistically proper sample selection is crucial for valid and accurate extrapolation from sample characteristics to general-population characteristics. The mathematical principles involved are rather simple and straightforward, but often are neglected in conducting surveys. Individuals within a target population or within a specified period must be selected on a random probability basis. Each individual must be identified in the sample frame (target popula-

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tion) and have a known chance of selection. All individuals in the frame should have an equal chance of selection or some greater, but known, chance than others of being selected and oversampled. The sample frame should make it possible to calculate the proportion of sampled individuals who participate in the study (i.e., provide the required data). Statistical formulas should be used to calculate the sampling error of an estimate based on the sample.

Three measurement approaches can be distinguished in population-based exposure assessments: direct, indirect, and questionnaire. In the direct approach, respondents report in time-use diaries and carry personal exposure monitors that record their exposures for short periods. In the indirect approach, exposure is imputed from the activities that respondents report in time-activity diaries. In the more traditional questionnaire approach, exposure is imputed from responses to self-reported factual questions or to general questions regarding activities. Time-activity data from representative diary studies can be used to calibrate or adjust personal-monitor data that are unrepresentative for the samples of people who cooperated in the study or for activity patterns that were affected by the presence of monitors. Diary data can be used to identify population groups whose activity patterns can lead to large exposures and to identify their special demographic features. A well-designed set of traditional questionnaire items might also help to identify high-risk populations and to predict exposure.

Almost all studies depend on some kind of traditional questionnaire to identify the background of respondents. The framing and wording of any questionnaire have a great effect on the responses to it and the inferences that are drawn from them. In general, the more standardized the question, the better it is for supporting inferences across studies. Recognizing the general need to develop reliable and valid questions for exposure-assessment, the committee proposed guidelines to improve question wording. The modification or adaptation of questions for particular study purposes could be done most effectively by persons trained in survey techniques.

The committee offers the following recommendations to foster the development of survey-research methods as effective tools for exposure assessment:

- Individual researchers should examine each survey question for its appropriateness for the purpose at hand. A trained survey methodologist can offer sound advice.
- More use can be made of less-expensive surveys conducted in communities or in sequential fashion (particularly given the high cost of personal-monitor studies).
- Basic research is needed on the reliability (precision) and validity (accuracy) of respondents' answers, especially for estimating frequency or dura-

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tion of exposure to various pollutants. Well-designed studies in a single community is an inexpensive way to develop more valid estimates.

- When the situations of high-exposure readings on personal monitors need to be identified more clearly, researchers should assess the feasibility and usefulness of having trained personnel observing respondents and collecting exposure data as unobtrusively as possible. Such a technique would require respondents' consent and selection of observation periods.

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Appendix A: Basic Standard Environmental Inventory Questionnaire[1]

[1]Source: Lebowitz et al., 1989b.

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Basic Standard
Environmental Inventory Questionnaire*

Basic Household Characteristics

Name of designated head of household: _____

Name of Respondent: _____

Home address: _____

Home phone: _____ Zip code: _____

Date: ___/___/___

This is a questionnaire for you to complete, regarding your present living quarters. Most of the questions asked are about the materials, appliances and furniture that are used within your home.

To record your response(s) circle ( ), check [ ] or write in the responses to each question. Please follow the arrows pointing to the side questions inside of boxes. For most of the questions in bold print, a "no" response will instruct you to "skip to" the next bold printed question. You can reach us at _____, or _____, if you have any questions.†

We appreciate your assistance in this study.

Your answers will be kept confidential and used for research purposes only.

Thank you for your cooperation.

Identification/Core Module For Proposed Standard E.I.Q.

A. Location Data

State _____ County _____ (2)†

Census tract _____ Block # _____ (5,5)

Street address: _____/_____ (20)
Apt./space #

City, zip _____/_____ (20,5-5)
Zip code

Name of respondent _____ (2)

B. Housing Characteristics

These questions are to determine the type of housing unit and living quarters in which your household lives. Circle one number only for each question.

* Base Elig. Final. 3/15/89

† Italicized terms refer to formats which are found on the original questionnaire. Further information for the Environmental Inventory Questionnaire are available from the Authors.

† Numbers in parentheses indicate field lengths

B1. How many rooms do you have in your living quarters?
(Do not count bathrooms, porches, balconies, foyers, halls, or half-rooms.)

Please Circle: 1 2 3 4 5 6 7 8 9+ (1)

B2. Are your living quarters—

1. Owned?
2. Rented?
3. Other? (1)

B3. Which best describes this building?
(Include all apartments, flats, etc., even if vacant.)

1. A mobile home or trailer
2. A one-family house detached from any other house
3. A one-family house attached to one or more houses
4. A building for 2 families
5. A building for 3 or 4 families
6. A building for 5 to 9 families
7. A building for 10 to 19 families
8. A building for 20 or more families
9. A boat, tent, van, etc.
10. Other, please specify: _____ (1)

B4. How many stories (floors) are in this building?
(Count an attic or basement as a story if it has any finished rooms for living purposes.)

1. 1 to 3
2. 4 to 6
3. 7 to 12
4. 13 or more stories (1)

B5. About when was this building originally built?
(Circle when the building was first constructed, not when it was remodeled, added to, or converted.)

1. 1986 to present
2. 1980 to 1985
3. 1970 to 1979
4. 1960 to 1969
5. 1950 to 1959
6. 1940 to 1949
7. 1939 or earlier
9. Don't Know (1)

B6. When did your household/family move into this house (or apartment)?

1. 1986 to present
2. 1980 to 1985
3. 1970 to 1979
4. 1960 to 1969
5. 1950 to 1959
6. 1940 to 1949
7. 1939 or earlier (1)

B7. How many bedrooms do you have?
(Count room used mainly for sleeping even if used also for other purposes.)

0. No bedroom
1. 1 bedroom
2. 2 bedrooms
3. 3 bedrooms
4. 4 bedrooms
5. 5 or more bedrooms (1)

B8. Where are cars/vehicles usually parked near your living quarters?
(Circle all that apply)

1. In an underground garage
2. In an attached garage
3. In an attached carport
4. On the street next to living quarters
5. Other (Specify): _____ (1)

C. Occupant Characteristics

The following questions describe the members of the household.

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C1. Number in household
(a) How many children under age 18 are there living in the Household?
____ Number of Children (2)

(b) How many adults, ages 18 and older, are there living in the Household?
____ Number ages 18–61 (2)
____ Number age 62 or more (2)

For the designated head of the household
(Please identify one person as the head and answer the following questions for this individual)

C2. What ethnic group (race) does this person consider themself? (circle one only)

1. White, Non Hispanic
2. Hispanic
3. Black
4. Asian
5. Other (specify): ____ (1)

C3a. What is the highest grade (or year) of regular school this person has ever attended?
(For example, completion of high school = 12)

____ Highest grade attended (2)

C4a. Does he/she have a paid job out of the home?

1. No, self employed in the home
2. No, full time homemaker
3. Yes, working full time
4. Yes, working part time
5. No, out of work just now but usually employed
6. No, a full-time student
7. Other, (specify): ____ (1)

C4b. Occupation
[ ] check here if this person has never worked outside of the home, and skip to next question.

1. What is or was his/her usual occupation? ____ (3)
2. What is his/her job title?: ____

For the respondent
(if not the Head of Household)

C5. What ethnic group (race) do you consider yourself? (circle one only)

1. White, Non Hispanic
2. Hispanic
3. Black
4. Asian
5. Other, (specify): ____ (1)

C6a. What is the highest grade (or year) of regular school that you have ever attended?
(For example, completion of high school = 12)

____ Highest grade attended (2)

C7a. Do you have a paid job out of the home?

1. No, self employed in the home
2. No, full time homemaker
3. Yes, working full time
4. Yes, working part time
5. No, out of work just now but usually employed
6. No, a full-time student
7. Other, (specify): ____ (1)

C7b. Occupation

[ ] Check here if you have never worked outside of the home, and skip to next question

1. What is or was your usual occupation? ____ (3)
2. What is your job title: ____

D. Smoking in the Home

1. Does anyone regularly smoke INSIDE OF YOUR LIVING QUARTERS?

1. Yes = Continue below
2. No = Skip to # E1 (1)

2. How many cigarettes, pipefuls, and/or cigars were smoked IN YOUR LIVING QUARTERS?

(a) During the most recent WEEK DAY:

____ # cigarettes ____ # pipes and/or cigars (5)

(b) During the most recent WEEK-END DAY:

____ # cigarettes ____ # pipes and/or cigars (5)

E. Cooking and Other Appliance Usage

E1. Cooking

(a) Do you have a gas range or oven?

1. Yes = continue below
2. No = skip to # E2 (1)

(b) Does your GAS range or oven have a continuously burning pilot light?

1. Yes 2. No (1)

(c) During the winter, do you ever use the range or oven to help heat the living quarters?

1. Yes, three or more days per week
2. Yes, one or two days per week
3. Yes, only in the morning to take the chill off (less than one hour)
4. No (1)

E2. Water Heater

(a) Is there a GAS water heater in your living quarters?

1. Yes = continue below # E2(b)
2. No = skip to Question # E3

(b) Where is your water heater located? (circle all that apply)

1. In a room within the living quarters, such as the kitchen.
2. In a closet or separate room in part of the main living quarters.
3. In a utility or closet room separate from the main living quarters.
4. In the garage.
5. In the basement.
6. Outside.
7. Other (please specify: ____ (1)

E3. Clothes Dryer

(a) Is there a clothes dryer in your living quarters?

1. Yes = continue below # E3(b)
2. No = skip to # E4

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Source: https://www.industrydocuments.ucsf.edu/docs/zxxj0001

F6. Which of the following best describes the construction of most of the lowest floor of the living quarters?

1. Concrete slab, uncovered
2. Tile, wood, or carpet over concrete
3. Earth, dirt, sand, or rock
4. Something else [SPECIFY _____] (1)

G. Organic Pollutants

G1. Have you worked with or used pesticides or herbicides outdoors for more than 1 hour at a time in the past 6 months?

1. Yes 2. No (1)

G2a. Did you or any member of the household, or a commercial applicator use pesticides in the living quarters in the past 6 months?

1. Yes
2. No → SKIP TO #G3a (1)

b. Specify Brand Names _____ (2)

_____

_____

c. Specifically, where are you using them?

1.	Living Room	4.	Master Bedroom
2.	Dining Room	5.	Other Bedrooms
3.	Kitchen	6.	Other Rooms (6)

G3a. In the past 6 months, were the drapes, carpeting, or furniture in your home steam or dry cleaned?

1. Yes No (1)

G4a. Are you now using mothballs or moth crystals in your living quarters?

1. Yes
2. No → SKIP TO #G5 (1)

b. Specifically, where are you using them?

1.	Living Room	4.	Master Bedroom
2.	Dining Room	5.	Other Bedrooms
3.	Kitchen	6.	Other Rooms (6)

G5. Do you store cleaning supplies (e.g., chlorine bleaches, detergents) in the following places?

1. Kitchen (1)
2. Basement (1)
3. Utility Room (1)
4. Bathroom (1)
5. Other (SPECIFY) (1)

_____

Human Exposure Assessment for Airborne Pollutants: Advances and Opportunities (1991)
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